International Journal of Academic Health and Medical Research (IJAHMR)
ISSN: 2643-9824
Vol. 7 Issue 11, November - 2023, Pages: 54-72

Lobular Carcinoma of the Breast: Clinical, Epidemiological, Anatomopathological and Therapeutic Profile (About 40 Cases)

M. Alami Merrouni, M. Benchaaboun, M. Bendahhou Idrissi, K. Saoud, N. Mamouni, S. Errarhay, C. Bouhchikhi, A. Banani

Department of Gynecology and Obstetrics I - Hassan II University Hospital Center of Fez.

Abstract: *Breast cancer is considered the leading cancer in women worldwide, with an increasing incidence, posing a real challenge for diagnosis and adequate management in developing countries. Currently, knowledge of its histological types, histoprognostic grades, and anatomoclinical stages increasingly influence its management. It is crucial to study the various types of breast cancer to refine therapeutic indications and improve survival rates, including lobular carcinoma, whose incidence has been rising in recent years. Invasive Lobular Carcinoma (ILC) represents 5 to 15% of breast cancers, making it the second most frequent histological type after invasive ductal carcinoma. In comparison to ductal carcinomas, in situ or invasive, lobular carcinomas, in situ or invasive, stand out due to diagnostic, therapeutic, and evolutionary peculiarities. Its uniqueness lies in the difficulty of clinical and mammographic diagnosis, its anatomopathological appearance, and its mode of proliferation, with a different metastatic dissemination pattern compared to invasive ductal carcinoma. The aim of our study is to specify the epidemiological, histological, clinical, paraclinical, therapeutic, and prognostic characteristics of lobular breast cancer based on our initial experience and a review of the literature. This is a retrospective study conducted at the Department of Obstetrics and Gynecology I of Hassan II University Hospital in Fez over a 4-year period from January 1, 2018, to December 31, 2022. We collected a total of 30 cases of women with invasive lobular carcinoma. The most affected age group was between 40 and 50 years, with an average age of 55.4 years. In 37.5% of cases, ILC was diagnosed at a late stage. The most frequent reason for consultation was the discovery of a nodule in 82.5% of cases, most often located in the upper outer quadrant (35%). In the majority of cases, it was the classical histological type, with a low Scarf-Bloom and Richardson (SBR II) grade (80%). Radical surgery, such as the Patey procedure, was performed in 82.5% of patients. Lymph node dissection was positive in 22 patients. Neoadjuvant chemotherapy was administered in 12 cases (30%), adjuvant chemotherapy in 15 cases (37.5%), and palliative chemotherapy in metastatic cases. Other adjuvant treatments included radiotherapy in 27 cases (65%), adjuvant hormone therapy in 34 cases (85%), and adjuvant targeted therapy in 6 cases (15%). The outcome was marked by 5 cases of metastases (pulmonary, bone, and hepatic), with 3 resulting in death. Invasive lobular carcinoma of the breast remains rare, with a unique clinical-pathological profile. Its clinical and radiological diagnosis is challenging. Currently, its treatment and prognosis do not differ from that of invasive ductal carcinomas.*

Keywords: cancer, breast, lobular, risk factors, pathological anatomy, surgery, survival.

INTRODUCTION:

Breast cancer is the most prevalent type of cancer among women, making it a significant challenge in terms of diagnosis and treatment [1]. According to the WHO, approximately one in 12 women develops breast cancer in their lifetime. The majority of cases (80 to 85%) are ductal carcinomas, while the remaining 15 to 20% are lobular carcinomas [2]. Frequently bilateral, breast cancer has a slow progression, which tends to give it a better prognosis than other invasive breast cancers. However, its diagnostic complexity and resistance to certain treatments can complicate matters [2]. In fact, invasive lobular breast cancer is challenging to observe through medical imaging (such as ultrasound and MRI), which can delay its diagnosis and treatment. It also appears to be less responsive to chemotherapy than ductal cancer. Ultimately, the prognosis of invasive lobular breast cancer is very comparable to that of other invasive breast cancers. The goal of our work is to specify the epidemiological, histological, clinical, paraclinical, therapeutic, and prognostic characteristics of lobular breast cancer through the analysis of 40 cases collected at the gynecology and obstetrics department of the Hassan II University Hospital in FES during a 6-year period from January 1, 2017, to December 31, 2022.

MATERIALS AND METHODS:

The purpose of our work is to clarify the epidemiological, histological, clinical, paraclinical, therapeutic, and prognostic characteristics of lobular breast cancer based on our initial experience and a review of the literature. This study is an epidemiological, descriptive, and retrospective analysis of different cases of lobular breast carcinoma followed in the Obstetrics and Gynecology Department I at the Hassan II University Hospital in Fes over a period of 6 years, from January 1, 2017, to December 31, 2022. We included all patients with lobular breast carcinoma during the study period, regardless of their age, and excluded breast tumors without histological evidence.

RESULTS:

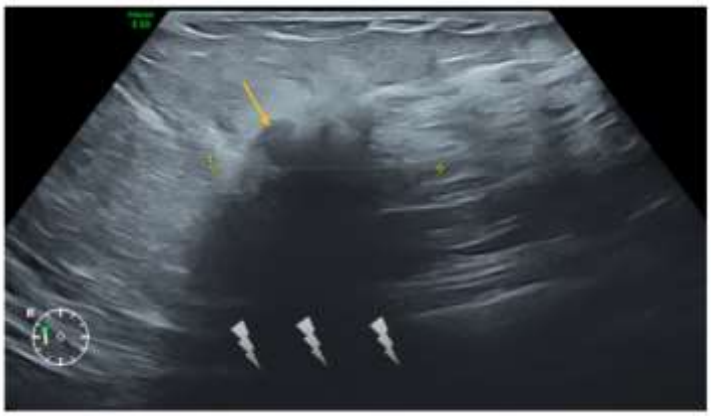
The average age of our patients is 55.4 years, ranging from 34 to 79 years. The most affected age group is between 60 and 70 years, accounting for 35% of cases. Eight women were using hormonal contraception, which is 20%, while 32 were not using

oral contraceptives (80%). The duration and type of contraceptive pill were not specified due to a lack of data. In our series of 40 patients, 27 were postmenopausal, making up 67.5%, and 13 were still in their reproductive years, which is 32.5%. The average age of menopause was 46.7 years, ranging from 45 to 57 years. Based on patient interviews, only one patient had a personal history of benign breast disease. None of the patients had a personal history of breast cancer, and four patients (10%) had a family history of breast cancer.

The time between the onset of the first symptoms and the date of consultation was specified for all patients. There was a delay in consultation for 15 patients, which is 37.5% of cases, after 6 months. The majority of patients (50% of cases) consulted within 3 to 6 months. In our study, the average delay was 5 months, with a minimum of 1 month and a maximum of 36 months. The most common reason for consultation in this series was the discovery of a breast lump in 33 cases, accounting for 82.5%, followed by mastodynia in 3 cases and signs of cutaneous inflammation in 2 cases. One patient consulted due to the palpation of an axillary lymph node, and another patient discovered it incidentally during a screening mammography.

Clinical breast examination revealed a palpable lump (alone or in combination with other signs) in 100% of cases. There was a left-sided predominance in 22 patients, accounting for 55%. The right breast was affected in 16 patients (40%), and 2 patients (5%) had bilateral involvement. The upper outer quadrant was the most common location for breast nodules in our patients, with a rate of 35%, followed by involvement of the junction of the upper quadrants, with a percentage of 20%. In our study, 45% of patients had tumor sizes between 2 and 5 cm, while sizes > 5 cm accounted for 30%. Ten patients had tumor sizes less than or equal to 2 cm. The consistency of the nodules was specified in 40 patients, with a hard texture found in 52% of cases. Nipple retraction was found in 4 patients, signs of inflammation in 3 patients, skin retraction in 2 patients, and one patient had skin ulceration. Palpation of axillary lymph nodes revealed homolateral lymphadenopathy in 11 patients, accounting for 27.5%. Among these, 9 patients had mobile lymph nodes, while 2 patients had fixed homolateral lymph nodes.

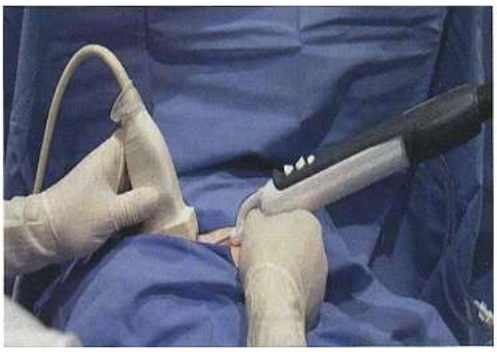
Mammography was performed for all patients, and 92.5% of mammography exams revealed at least one suspicious radiological breast opacity. Microcalcifications were found in 7 patients, accounting for 17.5% of cases. Bifocal and multifocal lesions were found in 5 patients, which is 12.5%. These different images were classified using the ACR (American College of Radiology) classification, with 35% classified as ACR4 and 62.5% as ACR5. Breast ultrasound was conducted for all patients and showed hypoechoic and/or heterogeneous formations with indistinct borders, possibly with signs of attenuation, in 36 cases (90%). Microcalcifications were found in 5 cases (12.5%), subcutaneous tissue thickening in 7 cases (17.5%), cystic formations in 4 cases (10%), axillary lymph nodes in 17 cases (42.5%), multifocality in 2 cases (5%), and bilaterality in 1 patient (2.5%). Magnetic resonance imaging (MRI) was performed for 7 patients and revealed a suspicious tissue mass in all cases. Among these MRI results, 6 were classified as ACR 6, and 1 was classified as ACR 4 (according to the ACR MRI Breast Imaging-Reporting and Data System, BI-RADS).



Breast ultrasound showing a large, poorly defined, spiculated, very hypoechoic mass in the upper-outer quadrant (UOQ) of the right breast, categorized as ACR5.

All patients, 100%, underwent breast biopsies for histological confirmation before starting treatment. The diagnostic certainty of lobular breast carcinoma was achieved through the histopathological study of the tumor, allowing the determination of grade and histological subtype. This study was conducted after Trucut breast biopsies in 37 patients, accounting for 92.5%, and tumor excisions in 3 patients, which is 7.5%. The histopathological study concluded that all patients had invasive lobular carcinoma, with 2 patients (10%) also having invasive ductal carcinoma. Lymph node dissection was performed on all operated patients, and lymph node involvement was found in 18 patients, representing 45% of operated patients. Among the 18 cases with positive lymph node involvement, 7 cases showed capsular rupture, accounting for 38.8%. Histologically, 60% of tumor sizes ranged from 2 to 5 cm. 13 patients (32.5%) had tumors smaller than 2 cm, and 3 patients had tumors larger than 5 cm. There were 9 cases of vascular emboli, which is 22.5% of the cases. Lobular carcinoma in situ (LCIS) was associated with the infiltrating component in 26 cases,

accounting for 65%. The SBR grade (Scarff-Bloom-Richardson) was specified for all patients, with the majority being SBR II in 32 cases (80%), followed by SBR III in 4 cases (10%), and SBR I in 4 patients as well. Among the patients who received neoadjuvant chemotherapy, the Chevalier grade was specified for 13 patients, all of which were classified as Grade 3. Hormone receptor status for estrogen and progesterone was determined for all patients, and 92% had positive estrogen and progesterone receptors. HER2 was positive (+++) in 12 cases, representing 30%. HER2 was negative (+) or (++) with negative CISH or FISH in 28 cases, accounting for 70%. Ki67 expression was evaluated in Grade II SBR patients, with Ki67 < 20% in 20 cases (62.5%) and > 20% in 12 cases (37.5%).



Equipment tray for microbiopsies.
Guided macrobiopsy using an automatic gun.

The locoregional staging primarily involved clinical examination to check for deep (pectoral) tumor fixation using the TILLAUX maneuver, which was found in 7 patients. Superficial (cutaneous) fixation was noted in 6 patients. Examination of the contralateral breast was systematically performed and was normal for all patients. Palpation of lymph node areas revealed mobile homolateral axillary lymph nodes in 9 patients and fixed homolateral axillary lymph nodes in 2 patients. General staging included the search for functional and physical signs of metastatic spread, which revealed bone signs in 2 patients, respiratory signs in 1 patient, no digestive signs in any patient, no neurological signs in any patient. It also included paraclinical examination including chest X-ray ; systematically performed for all patients, showing features suggestive of pulmonary metastases in 2 patients and being normal for 38 patients, abdominopelvic ultrasound ; conducted for 35 patients, showing suspicious malignancy features in 2 patients and being normal for 33 patients, bone scintigraphy ; performed for 20 patients, indicating secondary bone lesions in 2 patients, TAP CT scan; conducted for all patients, revealing secondary (hepatic/pulmonary) locations in 6 patients. Tumor markers (CA15-3): CA15-3 levels were measured for 4 patients, with elevated levels in only 1 patient and normal levels in 3 patients.

Regarding the TNM classification, T2 tumors were the most frequent, found in 28 patients in our series, accounting for 70%. N1 classified tumors were the most common among lymph node statuses, present in 8 patients, which is 20%. 5 patients had N3 classified tumors, representing 12.5%, and 4 patients had N2 classified tumors, making up 10%. In our series, 6 patients presented with metastases, which corresponds to 15% of our series. Only 1 patient was classified as stage I, accounting for 2.5% of cases. 21 patients were classified as stage II, making up 52.5% of cases. 12 patients were classified as stage III, representing 30% of cases. 6 patients were classified as stage IV, which is 15% of cases.

Breast cancer treatment is multimodal, based on the combination of locoregional and systemic treatments. Locoregional treatment involves surgery and radiotherapy, while systemic treatment includes chemotherapy and/or hormone therapy and targeted therapy. A weekly multidisciplinary consultation meeting is regularly held at the department, and a decision is made for each patient during this meeting. Radical surgery, such as Patey-type surgery, was performed in 33 cases, accounting for 82.5% of our series. Conservative surgery, in the form of tumorectomy with axillary lymph node dissection, was performed in 7 patients, making up 17.5% of cases. Adjuvant chemotherapy was administered to 15 patients, using the 4 AC 60 + 12 PACLI regimen. Neoadjuvant chemotherapy was given before locoregional treatment, mainly for advanced forms (T3, T4, and inflammatory). This chemotherapy was performed in 13 patients, representing 32.5%. Palliative chemotherapy was not administered to any patient. Among the 12 HER2+ cases, only 6 patients (15%) received Trastuzumab as an adjuvant treatment, with an initial dose of 8 mg/kg and a maintenance dose of 6 mg/kg for a total of 18 cycles. Conformal external radiotherapy was conducted for 27 patients, accounting for 67.5%. 18 patients received radiotherapy with 50 Gy to the breast wall after Patey and 46 Gy to the supraclavicular lymph nodes, with a conventional fractionation of 2 Gy per session and 5 sessions per week. 7 patients underwent systematic radiotherapy after conservative treatment, with radiotherapy at a dose of 50 Gy to the breast and 46 Gy to the lymph nodes, along with a 16 Gy boost to the tumor bed using electrons. In adjuvant therapy, 34 patients (85%) received hormone therapy. Tamoxifen was used in 21 cases (61.8%) at a dose of 20 mg per day, taken once daily for 5 years. 13 patients were treated with anti-aromatase drugs, accounting for 38.2% of cases.

Operative specimen from a Patey procedure for breast cancer.

In our series, we observed complete remission in 14 patients, accounting for 35% of cases. 3 patients were lost to follow-up. 5 patients developed metastases (bone/liver/lung). 18 patients, representing 45% of cases, are still undergoing treatment (radiotherapy or hormonal treatment) with favorable progress. We recorded 4 cases of death in our study, and the cause of their death was not specified. Additionally, all these patients had metastatic forms.

DISCUSSION:

The average age among women with invasive lobular carcinoma varies according to different studies. Ciobanu et al. found an average age of 58 years (range 45-69 years), with a slight tendency for non-classical forms to develop in older individuals [6]. In the Maghreb region, the average age was 51 years in Tunisia according to Khlifi [7] and 49.8 years in Morocco according to Bourgane [8]. In the Korean population, a study by Jung et al. [9] reported an average age of onset for these tumors at 48.4 years. In more recent studies, Bergaoui reported an average age of 53.43 years (range 45-69 years) [10]. In your series, the average age of your patients is 55.4 years, with extremes ranging from 34 years to 79 years. The most affected age group falls between 60 and 70 years, representing 35% of the cases.

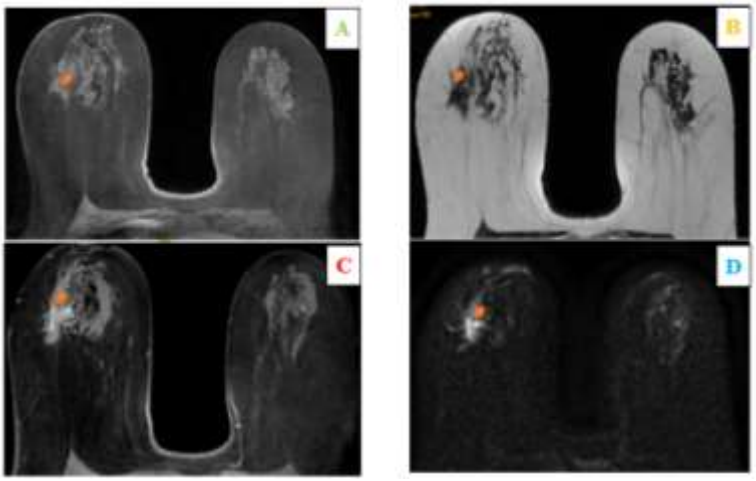
Concerning the risk factors, the literature data unanimously attribute an important role to age at first pregnancy and the number of children in the genesis of breast cancer. While the risk of breast cancer increases with a late first pregnancy, it appears to decrease if the first pregnancy occurs before the age of 30 [11, 12,13]. Indeed, pregnancy exerts a long-term protective effect due to the differentiation it induces in the mammary gland, making it less sensitive to carcinogens [14]. The number of children, especially if the patient had them at a young age, also seems to have a protective role [14]. In our series, the results are inconsistent with the literature as nulliparity represents only 15%, while the rate of multiparity is 67.5%. Regarding the age of menopause, a late age exposes to an increased risk of breast cancer due to prolonged estrogen secretion, especially during perimenopause [15,16]. In our series, 67.5% of the patients were menopausal. The age of menopause ranged from 45 to 55 years with an average of 46.7 years. Breastfeeding has often been considered a protective factor. A study showed that women who breastfed for a total duration of at least 25 months had a reduced risk of 33%, compared to those who never breastfed [17]. Several hypotheses have been proposed regarding the potential effect of lactation. On a hormonal level, there is an increase in prolactin and a decrease in estrogen production, which could have a suppressive effect on the mechanisms of breast carcinogenesis [18,19]. Among the 40 cases, 30 were breastfeeding, accounting for 75% of the cases, although the duration of breastfeeding was not specified in our study. Several studies have demonstrated a causal link between hormone replacement therapy (HRT) and the occurrence of infiltrating lobular carcinoma (CLI), as it increases the risk of this condition by 2 to 3 times more significantly than for ductal carcinoma in situ (CINS) [20]. Reeves et al. found a relative risk of 2.25 (CI: 2.00-2.52) for lobular cancers in postmenopausal women using HRT [21]. Interestingly, in the United States, there has been a simultaneous increase in HRT use and the incidence rate of CLI, supporting the hypothesis that

HRT elevates the risk of developing infiltrating lobular carcinoma [22,23]. However, in the current study, this hypothesis was not supported as none of the patients received hormone replacement therapy. Benign breast disease history, such as fibrocystic mastosis or lobular hyperplasia, particularly proliferative and atypical mastopathies, is associated with an increased risk of breast cancer. Dupont and Page, in a study involving 1,835 patients [24], demonstrated that adenofibroma was a long-term risk factor for breast cancer development. These cancers can be of any type, including ductal or lobular, invasive or "in-situ." In the study, only one patient had a personal history of benign mastopathy. CLI is associated with a family history of breast cancer in 6 to 17% of cases [25]. Several authors indicate an increased frequency of lobular carcinoma associated with family histories, especially on the maternal side [26,27]. According to the study conducted by Rosen et al. [25], patients were more likely to have lobular carcinoma if a sister was treated for breast cancer. In Khlifi's study [7], 8.1% of patients had a family history of breast cancer, while in Bourgane's study [8], this rate was 25% of cases. In Bergaoui's study [10], only one patient (3.33%) had a family history of breast cancer. In the current study, four patients had a history of lobular carcinoma in situ, accounting for 10% of cases.

The time interval between the onset of the first symptoms and the initial consultation can vary among cases. The mean consultation time according to Rosen et al. [25] was 3 months, and 2.7 months according to Anderson [28]. In the Maghreb region, the average consultation time was 7.8 months for Khlifi [7], 6 months for Bergaoui [10], and 11.65 for Bourgane [8]. In the present study, the average consultation time was 5 months, with a minimum of 1 month and a maximum of 36 months. Only 12.5% of these patients consulted within the first 3 months. Comparing these results with the literature reveals that patients in this study took longer to seek medical attention than those in American series. This delayed consultation time explains the often advanced stage of diagnosis. Lobular cancer is generally pauci-symptomatic and less conspicuous than ductal carcinoma. This leads to a delayed diagnosis [29]. It is frequently identified through a poorly defined, bulky, and difficult-to-palpate mass [1,2]. In a study by Cao et al. [30], the tumor was discovered through self-palpation in 84.9% of cases, nipple discharge in 1.9%, and 13.2% of patients had only microcalcifications on mammography. According to IDHAJOUB [31], self-palpation of a breast nodule was the most common reason for consultation, with a rate of 74.4%. Similarly, Bergaoui [10] reported a rate of 83.33%. In this study, self-palpation of a breast nodule was the most frequent method of CLI discovery, accounting for 82.5%, in line with the literature.The majority of medical societies and public health authorities consider the balance of benefits and risks to favor breast cancer screening and recommend systematic mammography screening for women aged 50 to 69. Early detection through screening remains the most critical method for combating breast cancer. As a result, the diagnosis of in situ carcinoma or atypical breast hyperplasia is becoming more frequent, attributed to early consultation for previously neglected clinical signs and an increase in screening examinations. In the presented series, a preponderance of left-sided breast cancer, particularly in the supero-external quadrant (QSE), was noted, consistent with literature data. CLI is known to be frequently bilateral compared to other types of breast cancer, either simultaneously or sequentially. Several authors have observed a high incidence of contralateral tumors in patients with CLI. According to Arpino et al. [3], a contralateral breast cancer was found in 20.9% of CLI cases compared to 11.2% in invasive ductal carcinoma (CCI). In the current series, a bilateral involvement was observed in 2 patients, constituting 5%. In terms of tumor size, infiltrating lobular carcinoma is characterized by larger tumor sizes at diagnosis. This can be attributed to a less pronounced or even absent stromal reaction, leading to insidious breast gland infiltration without the formation of a tumor mass, rendering the lesion impalpable and invisible, both clinically and on mammography [3, 39]. Many authors have observed larger tumor sizes at the time of diagnosis for lobular carcinomas compared to ductal carcinomas. Arpino et al. [3] analyzed 4,140 cases of CLI and 45,169 cases of CCI, with 54% of CLI patients having tumor sizes greater than 2 cm, compared to 49% of CCI patients. Among them, 14% of CLI patients had tumor sizes exceeding 5 cm, compared to only 9% of CCI patients. The results of Pestalozzi's study [40] align with those of Arpino, with a tumor size greater than 2 cm found in 55.1% of cases. According to IDHAJOUB, 65% of patients had tumor sizes between 2 and 5 cm, while sizes > 5 cm accounted for 24%. In the current study, 45% of patients had tumor sizes between 2 and 5 cm, while sizes > 5 cm accounted for 30%. Axillary lymph node involvement is considered one of the major factors predicting survival in patients with invasive breast cancer. Survival tends to decrease with an increasing number of lymph node metastases. The number of affected lymph nodes is also crucial in making decisions about adjuvant treatment. Although infiltrating lobular carcinomas tend to be diagnosed at a more advanced stage than invasive ductal carcinomas, and despite their larger size, it has been noted that the rate of lymph node involvement is similar or even slightly lower in comparison with that of invasive ductal carcinoma [3, 41, 42]. According to BOULAAMANE and ALOUANI [44, 43], homolateral axillary lymphadenopathy (N+) was found in 42% and 51.66% of cases, respectively. However, according to IDHAJOUB [31], this rate was around 15%. In the current study, the examination of lymph node areas identified mobile homolateral axillary lymphadenopathy in 27.5% of patients.

Mammography is a crucial examination that is recommended whenever clinical symptoms are present. Several studies have assessed the role of mammography in infiltrating lobular carcinoma (CLI) [45, 46, 47, 48]. All of these studies have reported the distinctive difficulty in detecting this histological variety, making mammographic screening more uncertain. It has been mentioned that mammography's sensitivity for lobular breast carcinoma ranges between 57% and 81% [45, 49, 50], with false-negative rates typically varying in the literature between 19% and 43% [46, 51, 52]. This has sparked interest in alternative imaging modalities such as ultrasound, magnetic resonance imaging, tomosynthesis, and targeted molecular imaging [53]. The most commonly encountered features include spiculated mass with dense center, spiculated mass with non-dense center, isolated architectural distortion, focal density asymmetry, multifocality and microcalcifications. Ultrasound is an essential complementary examination to mammography and clinical assessment for breast lesion evaluation. It aids in enhancing the diagnosis by showing a tumor mass or

a suspicious lesion and allows for echo-guided biopsies and aspirations to improve diagnostic accuracy. The sensitivity of ultrasound for detecting infiltrating lobular carcinomas (CLI) is better than mammography, with sensitivity ranging from 68% to 98%. However, the false-negative rate can be as high as 12% [60]. In your series, breast ultrasound was performed in addition to mammography for all patients. It revealed hypoechoic, heterogeneous images with indistinct borders, and signs of attenuation in 90% of the patients. Microcalcifications were found in 12.5% of cases, and skin thickening was observed in 17.5% of cases.Ultrasound also plays a vital role in the preoperative diagnosis of axillary lymph nodes by identifying lymph nodes with suspicious morphological characteristics. In your study, ultrasound detected axillary lymph nodes in 17 cases, representing 42.5%. On rarer occasions, in the absence of certainty about the presence of an anomaly in the two previous examinations, breast magnetic resonance imaging (MRI) may be proposed. MRI can be useful for differentiating between benign and malignant anomalies. It's a validated technique in the assessment of breast cancer extension, looking for multicentricity, multicentricity, and bilaterality, or for measuring the size of a poorly defined tumor in mammography. The unique characteristics of infiltrating lobular carcinoma make MRI a promising choice in this regard. Gest's study aimed to determine the discrepancies between sizes measured using breast MRI and histological size in CLI lesions. Results showed that if a numerical difference of 5 mm or more was taken between the sizes measured on MRI and histologically, as in the work of McGhan LJ et al, 45% of MRI measurements were concordant with histological results, 24.8% were underestimated, and 30.5% were overestimated. In your study, MRI was performed on 7 patients and identified suspicious tissue masses in all these cases. Among new imaging techniques, angiomammography, or digital mammography with iodine-based contrast agent injection, may have a place in breast cancer assessment. The advantages of this technique include a very short examination time (6 to 7 minutes), easy and rapid image analysis, and easy comparison with mammography. In your study, an American College of Radiology (ACR) classification was used to classify mammography images based on their level of pathological suspicion. This classification comprises six degrees ranked from 1 to 6 according to malignancy probability. It is complemented by other techniques like ultrasound, guided sampling, and possibly MRI due to its moderate specificity. The ACR's goal was to standardize the approach to each mammographic appearance. The classification ACR has significantly improved breast imaging practices.



Breast MRI showing a tissue mass in the upper-outer quadrant (UOQ) of the right breast with irregular contours described as low signal intensity on T1 FAST SAT, intermediate signal on T2, enhanced late after contrast, and restricted diffusion, corresponding to the previously described mass on ultrasound, classified as ACR5.

Ultrasound-guided breast biopsies can be performed using an automatic gun (micro biopsy) or a vacuum-assisted system (macro biopsies). They serve as an alternative to surgical diagnostic biopsies, confirming the benign nature of a subclinical lesion or fully characterizing a malignant lesion. These biopsies are an integral part of the pre-therapeutic strategy, helping in treatment planning [72]. The indications for these percutaneous sampling procedures are based on the ACR classification recommended by ANAES. The majority of indications are for ACR 4-classified abnormalities. Biopsies performed for ACR 5-classified images are becoming more frequent as part of an optimization strategy for therapeutic management. ACR 3 is the category that poses the most interpretation problems in practice [76]. Recent series in the literature show that this technique has a sensitivity ranging from 92% to 100% and a specificity of 95% to 100% [73]. Sensitivity and specificity increase with needle caliber (14G and 11G), shot length (in the case of automatic gun sampling), the number of samples, ultrasound guidance compared to stereotactic guidance, for solid nodules compared to microcalcifications, and with macro biopsies (10 or 11G) compared to micro biopsies (14G). Preceding guided biopsies increase the positive predictive value of surgical biopsies beyond 50%. They also improve the quality of excision and

significantly increase the rate of cases where surgical margins are clear from the beginning and do not require further surgery. In your series, breast biopsy was performed on all patients.

The unique feature of CLI lies in its pattern of metastatic spread. According to Chann et al [77], CLI can extend to unusual sites such as the peritoneum, retroperitoneum, and hollow viscera. CLI is characterized by diffuse infiltration of these organs, similar to lymphomas. These particular metastatic sites are typically observed at a late stage and may go unnoticed clinically [77]. The goal of this assessment is to detect metastases that could alter the therapeutic approach. In CLI, de novo metastatic forms are rare. According to Fondriner et al. [78], de novo metastatic forms were found in 0.5% of cases. In Bergaoui's series [10], only one patient presented with metastatic disease (hepatic localization), representing 3.33%. In your series, metastases at the time of diagnosis were found in 2 patients. Clinical examination is crucial for evaluating both local and general extension. Locoregional examination looks for tumor fixation to the deep plane (pectoral) using the TILLAUX maneuver, fixation to the superficial plane (cutaneous), contralateral breast involvement, axillary lymphadenopathy and its characteristics, and the presence of inflammatory signs. The staging workup, as per the 2013 NCCN GUIDELINE VERSION, includes bone scintigraphy, hepatic ultrasound to identify focal lesions, and standard chest radiography to reveal mediastinal, pulmonary, pleural, or parietal lesions. These initial exams aim to identify potential metastatic spread [79]. Further investigations such as thoraco-abdominal CT scans and bone scintigraphy, as well as FDG-PET-CT, may also be indicated to search for metastases that could influence the therapeutic approach. Hepatic metastases are diagnosed through ultrasound, CT scans, and guided biopsies when isolated lesions are discovered due to the frequent false positives of ultrasound [80]. Pleuro-pulmonary metastases are identified through chest radiography. Chest CT is more sensitive for small lesions [80]. Bone metastases are detected using bone scintigraphy, which is the most sensitive imaging method, possibly supplemented by standard X-rays. MRI and bone biopsy come into play as a second option, with the former used to clarify the extent of a bone lesion and its potential complications (medullary compression), and the latter for diagnosing isolated lesions [80].

Biological screening can only be effective if the marker can detect the disease at a curable stage in asymptomatic individuals. This is not the case for CA15-3, which is elevated only in 30% of cases at the time of diagnosis and cannot be used for screening purposes. Due to its low sensitivity, CA 15-3 is not a reliable tool for diagnosing lobular breast carcinoma biologically. It is not useful in the diagnosis and monitoring of lobular carcinomas in situ but does have relevance in the postoperative monitoring of invasive lobular carcinomas. The CA 15-3 level before any treatment serves as an essential reference value for future monitoring. Therefore, the initial CA 15-3 level is a recognized prognostic factor. The risk of later metastasis is 67% for patients with an initial level over 30 kU/L, 83% for a level exceeding 40 kU/L, and an initial value over 50 kU/L should prompt a search for potential metastasis [81].

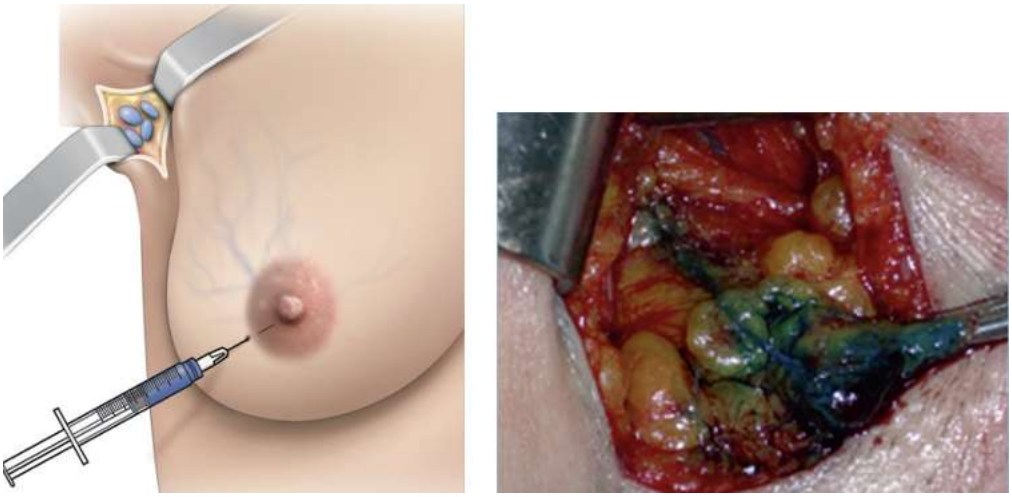
The current approach to adjuvant treatment decisions for breast cancer is based on the molecular classification of tumors. These decisions consider various molecular factors, potential comorbidities, and patient preferences, which collectively determine the need for adjuvant chemotherapy and its specifics. The Saint-Gall Conference in 2011 recommended various systemic treatments based on molecular classification.There are five distinct subtypes:

- Luminal A: This subtype shows strong expression of estrogen and progesterone receptors while being HER2-negative. It also exhibits positive luminal cytokeratins (8, 18, 19) and GATA3 gene expression, with low proliferation-related gene expression. Luminal A tumors have the best clinical outcomes and a favorable prognosis. They benefit from hormonal monotherapy.
- Luminal B: Similar to Luminal A in immunohistochemical profile but with lower estrogen receptor expression, HER2 overexpression, and higher proliferation-related gene expression. The increased proliferation in this subtype leads to a relatively higher risk of recurrence compared to Luminal A. Luminal B tumors, being hormonosensitive, may also require chemotherapy in addition to hormonal therapy, and they are candidates for trastuzumab treatment.
- HER-2 subtype: Characterized by strong expression of several genes from the ErbB2 amplicon (particularly GRB7) and a lack of estrogen receptors. It also has high proliferation-related gene expression and p53 positivity. This subtype is associated with a poor prognosis and resistance to hormone therapy, especially tamoxifen.
- Basal subtype: Corresponds to tumors lacking hormone receptors and HER2 (known as "triple-negative"). These tumors must express other basal markers, such as high molecular weight cytokeratins (5, 6, 14, 17), EGFR, or Ckit. They are typically mutated for p53 and have the least favorable prognosis, often affecting younger women with a peak risk of recurrence within the first two years.
- Normal subtype: This subtype is considered artifactual, resulting from contamination of tumor samples by normal breast tissues and is not clinically utilized.

In the series being discussed, the Luminal A subtype was the most common, accounting for 33%, followed by the Luminal B subtype at 26%, consistent with the majority of series' results.

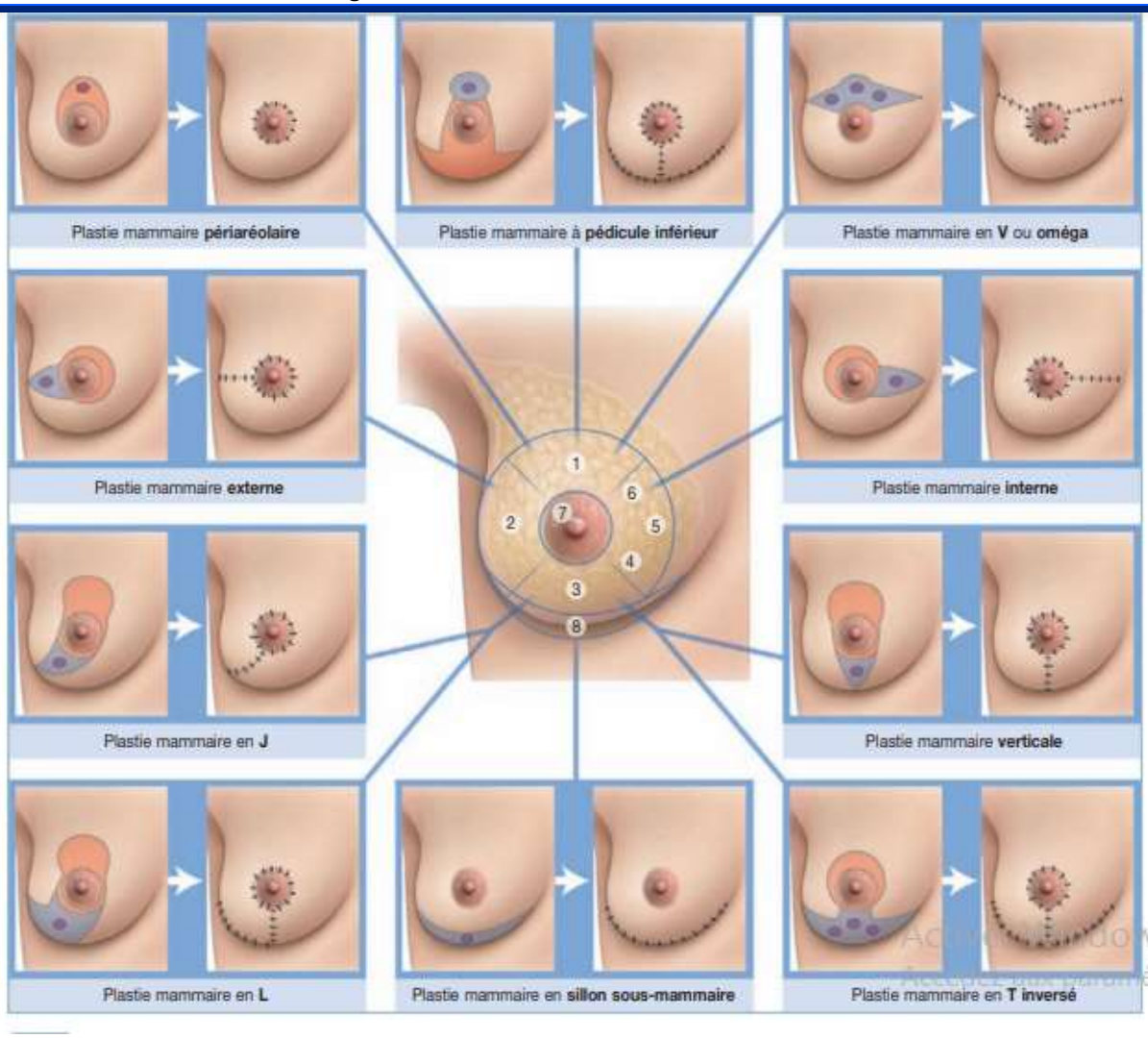
The treatment of lobular breast carcinoma is determined through a multidisciplinary approach, involving various medical professionals [82]. The primary treatment goals include achieving a high likelihood of cure, prolonged recurrence-free survival, satisfactory aesthetics, and cost-effective outcomes [82]. Surgical intervention is typically the first step in treating lobular breast carcinoma, and various techniques are employed based on the tumor's characteristics [83]. There are two surgical options for lobular breast carcinoma: lumpectomy (conservative) and mastectomy (radical), along with axillary lymph node dissection or

sentinel lymph node biopsy [83]. The choice between these two therapeutic options depends on factors such as the tumor itself and the patient's suitability [83]. While conservative treatment is accepted for most early-stage breast cancer, it's often questioned for lobular invasive carcinomas due to histological and clinical peculiarities [39, 127]. Some studies suggest that conservative treatment is suitable only for patients without specific characteristics, such as tumor size, lymphovascular invasion, multifocality, or young age [128]. Although some studies have indicated a higher risk of local recurrence with conservative treatment, recent research has not found a significant difference in local recurrence rates between conservative treatment and mastectomy [139, 140]. Axillary lymph node dissection plays an essential role in staging breast cancer and is crucial for local control [92]. Sentinel lymph node identification and removal are also vital for staging and treatment planning, with wider indications now extending to larger tumors and multifocal cases [92].



The injection of patent blue dye peri-areolar or peri-tumoral allows the visualization, after a 10-minute waiting period, of the blue-stained sentinel lymph nodes.

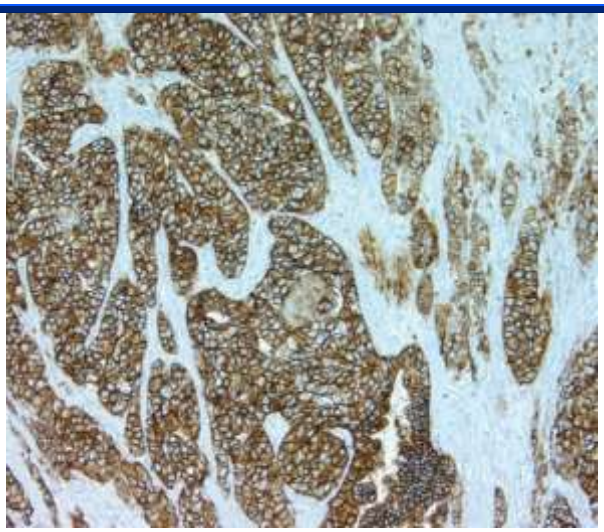
Oncoplastic surgery, a combination of plastic surgery techniques and breast cancer treatment, allows for a more conservative approach and better aesthetic outcomes. Radiation therapy is crucial in the management of lobular breast carcinoma, providing a significant reduction in local recurrences [100, 101]. Adjuvant radiotherapy after surgery improves local control and survival, with substantial benefits, especially in younger patients [143]. Adjuvant chemotherapy significantly reduces the risk of recurrence and death from lobular breast carcinoma, with the benefit proportional to the risk of recurrence [110, 111, 112]. Lobular invasive carcinomas are less responsive to chemotherapy than other types due to their unique immunohistochemical profile [149]. Hormone therapy is crucial for breast cancer cases expressing estrogen receptors, including lobular invasive carcinomas, which frequently have positive hormonal receptors [152]. Trastuzumab has been a significant advancement in the treatment of HER2+ breast cancer, reducing the risk of recurrence and improving survival [122]. Ongoing research explores targeted therapy options for lobular invasive carcinomas, such as FGFR1 amplification [157]. In conclusion, the choice of treatment for lobular breast carcinoma should consider the individual patient and tumor characteristics, and further research is needed to develop effective targeted therapies for this histological type [157].



Oncoplastic surgery techniques

In terms of prognostic factors, age is a significant prognostic factor for breast cancer. Invasive lobular carcinoma (CLI) typically occurs in older women, impacting their survival since older patients have a lower life expectancy [32,3]. Conversely, young age, especially in women under 35, is correlated with an unfavorable prognosis. This is due to a faster tumor proliferation, a high histological grade, lymph node involvement, more frequent vascular emboli, and often negative estrogen receptors [158]. The prognosis is better for localized forms compared to advanced ones. Tumor size, the primary parameter in the TNM classification, is directly related to metastatic status at the time of diagnosis and 5-year survival. At the time of diagnosis, lobular carcinomas are usually larger than ductal carcinomas, with a higher percentage of T3 lesions. Therefore, their latency period is likely longer [158]. Approximately 18% of invasive lobular tumors and 13% of ductal tumors are detected at stage II (T2N0) [105]. Some researchers have assumed that lobular carcinomas exhibit less aggressive behavior than ductal carcinomas [36,159]. Given the low incidence of lymph node metastases in CLI, the stage tends to progress from stage I to II primarily due to tumor size (T2 or larger) [160]. MORENO-ELOLA et al. [187] observed a low percentage of axillary lymph node metastases in lobular carcinomas (32%) compared to ductal carcinomas (37%), despite larger tumor size, indicating no correlation between tumor size (T) and axillary invasion (N). The literature reports a positivity rate of 2 lymph nodes for lobular carcinoma and 4.5 for ductal carcinoma at stage III [36, 161]. In conclusion, axillary lymph node status appears to exert a more significant influence than tumor size in the prognostic evaluation of invasive lobular breast carcinoma. The latter seems to be secondary [46, 162]. Identifying the histological variant is an important predictive element in assessing the prognosis of infiltrating lobular carcinomas. A detailed analysis of the histological subtypes of this disease has shown that the classic variant is associated with a more favorable prognosis. Orvieto E et al. [163] assessed the prognostic impact of histological subtypes in a series of 530 patients with invasive lobular carcinoma. They found an increase in distant metastases and a decrease in overall survival in patients with any histological variant of invasive lobular carcinoma compared to those diagnosed with the classic variant. The unfavorable prognosis of certain histopathological

variants of invasive lobular carcinoma had previously been identified by other authors, albeit based on a limited number of cases [32, 164]. The study by Du Toit et al. [165], involving the five subtypes of invasive lobular carcinoma (classic, tubulolobular, solid, alveolar, or mixed), aligns with previous research, revealing a significant difference in survival rates between tubulolobular and solid variants. The tubulolobular variant had the best prognosis among all other subtypes of invasive lobular carcinoma studied, and possibly even among breast cancers in general. However, the solid subtype had the worst prognosis.
In 2012, Lorfida M et al. [166] studied a series of 981 invasive lobular carcinomas (ILC) of the breast diagnosed at the European Institute of Oncology between 1994 and 2005. The solid and mixed subtypes showed a statistically significant difference, with an unfavorable prognosis compared to classic ILC.According to recent studies, the pleomorphic variant of invasive lobular carcinoma (ILC) is characterized by particular aggressiveness due to significant cytological changes, an increased tendency for peritumoral vascular invasion, reduced hormone receptor expression levels, and higher overexpression of the HER2 gene [163, 167, 168]. In conclusion, histopathological subtyping of invasive lobular carcinoma (ILC) is clinically relevant and provides valuable information for therapeutic decision-making, especially for ILC variants with particularly high aggressiveness. Tumor cell morphology and mitotic count vary significantly from one tumor to another, forming the basis for various histoprognostic grading systems. All studies demonstrate that metastatic risk and survival are closely linked to the grade of breast cancer, regardless of the classification scale used. Higher-grade tumors are associated with a poorer prognosis. Therefore, histoprognostic grade is an important and independent prognostic factor in breast cancer, significantly influencing overall survival [169]. Among the assessment methods, the Scarff-Bloom and Richardson (SBR) score (see Annex 3) is frequently used. Tumors classified as high-grade SBR III are considered to have a poor prognosis and are strongly associated with a high risk of metastasis to unfavorable sites such as the liver and lungs [162]. The majority of invasive lobular carcinomas (ILCs) are classified as grade 2 due to moderate nuclear pleomorphism and a low mitotic rate [168,170]. Classic ILC forms can be classified as grade 1, while pleomorphic lobular carcinomas may be classified as grade 3 if there are a sufficient number of mitotic figures present [171]. In our series, the rate of high-grade SBR II is noted in 80%, followed by SBR III in 10%, all of which were of the pleomorphic type. Axillary lymph node staging provides important prognostic information [173]. Numerous studies have concluded that patients with locoregional metastases have a poorer prognosis than those without lymph node involvement. Prognosis is also linked to the number of involved lymph nodes; the more nodes involved, the shorter the survival [172]. Mac Grogan et al. [174] reported that the uniform appearance of tumor cells in ILC, characterized by the absence of cellular atypia and a low mitotic rate, makes the detection of cancerous lobular cells in metastatic lymph nodes more challenging. Lymph node involvement is then underestimated for this histological type, with a high rate of false negatives, justifying more frequent use of immunohistochemistry in case of doubt [3]. For Fortunato et al. [4], the rate of lymph node involvement in ILC was 33%, while in our study, histological lymph node involvement (PN) was more common, with a rate of 47% of cases. The presence of vascular emboli is an unfavorable prognostic factor. In patients without lymph node involvement, their presence has been shown to be an independent risk factor. Furthermore, their presence promotes distant metastases and reduces the survival rate [175]. Additionally, the presence of these emboli is also a risk factor for local recurrence. Many authors report the less frequent presence of vascular emboli in ILC [7, 3, 176], which can be a favorable prognostic factor for this histological type. In our study, we observed 9 cases of vascular emboli, accounting for 22.5% of cases, which aligns with the data in the literature. By examining and analyzing the immunohistochemical prognostic factors of invasive lobular carcinomas (ILC), it is possible to predict the course of the disease and identify patients whose tumors will manifest aggressively. This approach allows for the adoption of the most appropriate therapeutic strategy for each patient [177]. Hormone receptors are considered prognostic factors, with these intracellular proteins binding to estrogen and progesterone being essential for the tumor to be hormone-sensitive. The study of the prognostic value of estrogen receptors (ER) shows a higher recurrence rate in ER-negative patients compared to ER-positive patients. While the prognostic value of progesterone receptors (PR) has been studied less, several studies have shown better 5-year survival for tumors expressing this receptor. In patients without lymph node involvement, the simultaneous presence of both estrogen and progesterone receptors is associated with a better prognosis than the absence of one or both receptors. Furthermore, these receptors are also predictive factors for the response to adjuvant hormonal treatments [178]. The majority of invasive lobular carcinomas exhibit high expression of estrogen and progesterone receptors, making them eligible for hormonal treatment, which can also improve the prognosis of the disease [3, 33, 179]. In the figure below, we compare the rates of hormone receptors found in our series to the literature data [42, 33, 149, 3, 180, 41]. The oncogene C-erbB-2, also known as HER-2 (Human Epidermal Growth Factor Receptor 2), is a protein located on the cell surface and involved in the regulation of cell growth. Amplification and/or overexpression of HER2 can contribute to cell transformation through a mechanism that enhances cell growth.
Amplification and/or overexpression of the HER2 receptor are found in 15 to 30% of breast cancers. Several studies have shown that the presence of HER2 overexpression and/or amplification in breast cancers is a sign of poor prognosis. Tumors that initially overexpress HER2 tend to be more aggressive, have a higher metastatic potential, and are less responsive to hormonal and/or chemotherapy treatments [181]. In invasive lobular carcinomas (ILCs), the expression and/or gene amplification of the HER2 protein are rare events. The pleomorphic variant of lobular carcinomas, especially grade 3, is an exception to this rule, with overexpression of the HER2 protein [182].



Tumor strongly expressing HER2 (Penault-Llorca et al., 2011).

According to ARPINO [3], only 5-10% of ILCs showed HER2 protein overexpression, primarily affecting ILC variants. In contrast, LEE [176] found HER2 protein overexpression in only 2.5% of cases. In our study, HER2 protein overexpression was noted in 30% of patients, most of whom had a variant form of ILC, which aligns with the literature data. Ki-67 is often used in histopathology to assess the rate of cell proliferation in cancer tissues. The amount of Ki-67 detected in cancer cells is often correlated with the tumor growth rate and disease prognosis. High levels of Ki-67 can indicate faster tumor growth and a poorer prognosis. The average positive value of Ki67 in breast tumors is 15%, and this figure is correlated with the grade, reaching the highest values in poorly differentiated tumors. Tumors lacking hormone receptors often have high Ki67 values, and there is a strong correlation between Ki67 expression and survival [167]. For invasive lobular carcinomas, the proliferation index is generally low, which is associated with better survival [183]. The E-cadherin protein is a transmembrane protein involved in cell-cell adhesion and acts as a suppressor of invasion. It has been identified as a reliable differentiation marker to distinguish between ductal and lobular breast carcinomas. E-cadherin protein expression is usually present in ductal breast carcinomas but absent in invasive lobular carcinomas. Its absence is important for diagnosing lobular carcinomas, and the use of immunohistochemistry for E-cadherin is helpful in addition to conventional histology. However, in rare cases of poorly differentiated ductal carcinomas (less than 15%), E-cadherin expression may be absent. In such situations, other morphological characteristics, such as tubule formation, along with additional tests for hormone receptors and immunohistochemistry, are necessary to confirm the diagnosis of E-cadherin-negative ductal carcinoma. An anti-oncogene, located on chromosome 17 at p13.1 and coding for a nuclear phosphoprotein, has been identified. Its overexpression has been significantly associated with an increased risk of local relapses in women who have undergone breast-conserving surgery without radiation therapy. According to JUNG [9] and ARPINO [3], invasive carcinomas with low expression of the P53 protein are associated with a favorable prognosis.

In most cases, optimally treated invasive lobular carcinomas have a favorable outcome [188]. MORENO-ELOLA et al. [187] conducted a descriptive multidisciplinary study, both retrospective and prospective, in various centers, with a population of 404 patients diagnosed with pure or mixed invasive lobular carcinoma. In this study, overall survival was 89.4% at 1 year, 86.1% at 2 years, 81.8% at 4 years, 77.2% at 6 years, and finally 65.5% at 8 years. The overall 10-year survival rate was 65%. MORENO-ELOLA et al. [187] concluded that the prognosis of invasive lobular breast carcinoma is favorable, with a survival rate of over 50% of patients after a follow-up duration of 17 years. Additional studies on this subject have corroborated the results of MORENO-ELOLA and confirmed the generally favorable trend in the progression of invasive lobular carcinomas [159, 189, 190, 191]. Locoregional recurrence occurs when invasive cancer reappears in the treated breast, axillary, supraclavicular, or internal mammary lymph nodes, before or at the same time as the appearance of distant metastases. To prevent this, surgeons must pay particular attention to respecting safety margins during lumpectomy. A significant correlation has been observed between the number of invaded lobules and the frequency of recurrences. This frequency increases when the number of invaded lobules is equal to or greater than 10 [192]. When local recurrence occurs, the time between initial treatment and recurrence is a significant prognostic factor for survival. Patients who experience local recurrence within two years following treatment have a shorter survival [3]. In Pestalozzi et al.'s study [40], the rate of local recurrence for invasive lobular carcinomas was not higher than the rate for invasive ductal carcinomas. However, the rate of contralateral recurrence was significantly higher in patients with invasive lobular carcinoma in Arpino's series [3]. Among the patients in our series, no cases of local recurrence were noted.The pattern of metastatic dissemination of invasive lobular carcinomas differs from that of invasive ductal carcinomas, as it metastasizes through both hematogenous and lymphatic routes. Common sites of metastases in invasive lobular carcinoma include the peritoneum, retroperitoneum, bones, meninges, stomach, gastrointestinal tract, bone marrow, and gynecological organs, while pleuropulmonary

metastases are less common [193]. Understanding the metastatic spread of invasive lobular carcinomas is crucial for interpreting imaging findings during staging to detect metastatic disease localization. In our series, 5 patients presented with metastases (bone/liver/lungs).

CONCLUSION:

While invasive lobular carcinoma (ILC) of the breast is a relatively rare form of cancer, the prevalence of breast cancer justifies a comprehensive understanding of its peculiarities. Lobular carcinomas account for 2.8% to 6% of malignant breast lesions, with a prevalence of 0.8% to 3.8% for in situ forms. Invasive lobular carcinoma, a type of invasive carcinoma, represents 4% of all invasive breast cancers and 10% of all breast cancers.

The clinical and pathological characteristics of ILC include increased tumor size, an increased risk of multifocality, multicentricity, and bilaterality, as well as a challenging diagnosis due to a lack of clinical and radiological specificity. Breast magnetic resonance imaging (MRI) should be used to assess conservative treatment options. Metastases from ILC are more common in the gastrointestinal serosa, stomach, ovaries, and meninges, making their monitoring problematic. Although the current treatment for ILC does not differ from that of invasive ductal carcinoma, there is a need for long-term survival and prognosis studies for ILC. The success of these studies will depend on collaboration among researchers from different disciplines, the quality of patient follow-up, and the archiving approach for patient management.

Conflicts of interest:

All the authors have no financial disclosure or conflicts of interest with the presented material in this presentation.

References:

1. Agwalt T, Cunnungham D, Hadjiminas D - Differences in presentation of lobular, ductal, mixed and special typa breast cancer. EJC Supplements. 2005 Sep;3 (1):21

2. H.Mersein E.Yildirim.K.Gulben And U. Berberglu - In invasive lobular carcinoma different from invasive ductal carcinoma ESJO 2003 : 390-395

3. Arpino, Grazia, Bardou, Valerie J., Clark, Gary M., et al. - Infiltrating lobularcarcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res, 2004, vol. 6, no 3, p. R149-R156.

4. Fortunato, Lucio, Mascaro, Alessandra, Poccia, Igor, et al. - Lobular breastcancer: same survival and local control compared with ductal cancer, butshould both be treated the same way? analysis of an institutional databaseover a 10-year period. Annals of surgical oncology, 2012, vol. 19, no 4, p.1107-1114.

5. Cristofanilli M, Gonzalez-Angulo A, Sneige N, Kau SW, Broglio K,Theriault RL,et al: Invasive lobular carcinoma classic type: response toprimary chemotherapy and survival outcomes. J Clin Oncol 2005, 23(1):414

6. Ciobanu, M., et al. "Breast invasive lobular carcinoma: a retrospectiveclinicopathologic study of 25 cases."Romanian journal of morphology andembryology= Revue roumaine de morphologie et embryologie 53.3 (2012): 533.

7. Khlifi, A., Ziadi, S., Trimeche, M., et al. - Étude clinicopathologique descarcinomes lobulaires du sein dans le Centre tunisien: à propos de 74cas. Journal africain du cancer/African Journal of Cancer, 2011, vol. 3, no 3,p. 155-162

8. Bourgane.L et al. Le carcinome lobulaire du sein : le profil épidémiologique, clinique, thérapeutique et évolutif à Marrakech à propos de 20 cas (128-16)

9. Jung, So-Youn, Jeong, Junsoo, Shin, Seung-Ho, et al. The invasive lobularcarcinoma as a prototype luminal A breast cancer: A retrospective cohortstudy. BMC cancer, 2010, vol. 10, no 1, p. 664.

10. Bergaoui Haïfa et al, Service de Gynécologie Obstétrique, Centre de Maternité et Néonatologie de Monastir, Tunisie 3 Le carcinome lobulaire infiltrant du sein: à propos de 30 cas

11. Negri E, La Vecchia C, Bruzzi P. Risk factors for breast cancer: pooledresults from three Italian case-control studies. Am J Epidemiol 1988;128:1207–15.

12. Tao SC, Yu MC, Ross RK. Risk factors for breast cancer in Chinese womenof Beijing. Int J Cancer 1988;42:495–8.

13. MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, et al. Ageat first birth and breast cancer risk. Bull WHO 1970;43:209–21

14. Russo J, Moral R, Balogh GA, Mailo D, Russo IH. The protective role ofpregnancy in breast cancer. Breast Cancer Res 2005;7:131–42

15. Alexander FE, Roberts MM. The menopause and breast cancer. EpidemiolCommun Health 1987;41:94–100.

16. Brinton LA, Schairer C, Hoover RN. Menstrual factors and risk of breastcancer. Cancer Invest 1988;6:245–54

17. Collaborative group on hormonal factors in breast cancer. Breast cancer and breastfeeding : collaborative reanalysis of individual data from 47epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease. Lancet 2002 ; 360 : 187-95

18. Key TJ, Pike MC.The role of estrogens and progestagens in theepidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol1988;24:29–43.

19. Byers T, Graham S, Rzepka T.Lactation and breast cancer: evidence for anegative association in premenopausal women. Am J Epidemiol1985;121:664–74
20. Reeves GK, Beral V, Green J, Gathani T, Bull D. Million Women Study Collaborators: Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and metaanalysis. Lancet Oncol. 2006;7(11):910-8
21. Newcomer LM, Newcomb PA, Trentham-Dietz A, Longnecker , Greenberg ER. Oral contraceptive use and risk of breast cancer by histologic type. Int J Cancer. 2003;106(6):961-4.
22. Hemminki, E., Kennedy, D., Baum, C., & McKinlay,S. (1988). Prescribingof Noncontraceptive Estrogens and Progestins in the United States, 1974-86. American Journal of Public Health, 78, 1478-1481.
23. Wysowski, D.K., Golden, L., & Burke, L. (1995). Use of Menopausal Estrogens and Medroxyprogesterone in the United States, 1982-1992. Obstetrics & Gynecology, 85(1), 6-10.
24. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD, RadosMS and Schuyler PA, Long-term risk of breast cancer in women withfibroadenoma, N Engl J Med, 1994, 331 : 10-15.
25. Rosen PP, Martin L, Lesser, et al (1982) Epidemiology of breast carcinomaIII.Relationship of family history to tumor type. Cancer 50:171–9
26. Vakil DV.Histologic and epidemiologic features of breast cancer. Am JEpidemiol 1977; 106:249.
27. Haagensen CD. Family history of breast carcinoma in women predisposed todevelop breast carcinoma. J Nail Cancer Inst 1972; 43:1025-1027
28. Anderson DE. Genetic study of breast cancer: Identification of a high riskgroup. Cancer 1974; 34:1090-109
29. Arpino, Grazia, Bardou, Valerie J., Clark, Gary M., et al. Infiltrating lobularcarcinoma of the breast: tumor characteristics and clinical outcome.Breast Cancer Res, 2004, vol. 6, no 3, p. R149-R156
30. Cao, A.-Yong, Huang, Liang, WU, Jiong, et al. Tumor characteristics andthe clinical outcome of invasive lobular carcinoma compared to infiltratingductal carcinoma in a Chinese population. World Journal of SurgicalOncology, 2012, vol. 10, no 1, p. 152
31. Fatima Ezzahra IDHAJOUB - Le carcinome lobulaire du sein : Le profil clinique, épidémiologique, anatomopathologique et thérapeutique au service de gynécologie obstétrique. Thèse 166 (2019)
32. Wasif, Nabil, Maggard, Melinda A., KO, Clifford Y., et al. Invasive lobularvs. ductal breast cancer: a stage-matched comparison of outcomes. Annals ofsurgical oncology, 2010, vol. 17, no 7, p. 1862-1869
33. Molland JG, Donnellan M, Janu NC, et al (2004) - Infiltrating lobularcarcinoma: a compar son of diagnosis, management and outcome with infiltrating duct carcinoma. Breast 13:389–96
34. M.L. Lesser, P.P. Rosen and D.W. Kinne, Multicentricity and bilaterality ininvasive breast carcinoma, Surgery 91 (1982),234–240.
35. P.L. Horn and W.D. Thompson, Risk of contralateral breast cancer. Associations with histologic, clinical, and therapeutic factors, Cancer 62 (1988), 412–424.
36. M.J. Silverstein, B.S. Lewinsky, J.R. Waisman et al., Infiltrating lobularcarcinoma. Is it different from infiltrating duct carcinoma Cancer 73 (1994),1673 1677.
37. DEDES, Konstantin J. et FINK, Daniel. Clinical presentation and surgicalmanagement of invasive lobular carcinoma of the breast. Breast disease,2008, vol. 30, no -1, p. 31-37
38. A.P. Polednak, Bilateral synchronous breast cancer: a population-basedstudy of characteristics, method of detection, and survival, Surgery 133(2003), 383–389
39. Sastre-Garau X, Jouve M, Asselain B, et al. Infiltrating lobular carcinoma ofthe breast. Clinicopathologic analysis of 975 cases with reference to data onconservative therapy and metastatic patterns. Cancer 1996;77:113–2
40.B.C. Pestalozzi, D. Zahrieh, E. Mallon et al.,Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of15 International Breast Cancer Study Group clinical trials,J Clin Oncol 26(2008), 3006–3014
41.Mersin H, Yildirim E, Gulben K & Berberoglu U 200 - Is invasive lobular carcinoma different form invasive ductal carcinoma European Journal of Surgical Oncology 29 390–395.
42. Korhonen T, Huhtala H & Holli K 2004 - A comparison of the biological and clinical features of invasive lobular and ductal carcinomas of the breast.Breast Cancer Research and Treatment 85 23–29
43. El Alouani, C., Khouchani, M., Benhmidoune, A., El Omrani, A., &Tahri, A. (2010). Caractéristiques clinicopathologiques, thérapeutiques et évolutives du cancer lobulaire du sein dans la région de Marrakech. Cancer/Radiothérapie, 14(6-7), 639. doi:10.1016/j.canrad.2010.07.567
44. Boulaamane, L., El Mejjaoui, S., Aassab, R., Ismaili, N., Lalya, I., Mahfoud, T., ... Errihani, H. (2010). Carcinome lobulaire infiltrant du sein : expérience marocaine à propos de 130 cas. Cancer/Radiothérapie, 14(6-7), 633. doi:10.1016/j.canrad.2010.07.550
45. Helvie MA, Paramagul C, Oberman HA, Adler DD - Invasive lobular carcinoma: imaging features and clinical detection. Invest Radiol1993; 3:202-7.
46. Krecke KK, Gisvold JJ. - Invasive lobular carcinoma of the breast: mammographics findings and extent of disease at diagnosis in 184 patients.AJR 1993;161:957-60.

47. Hilleren DJ, Andersson IT, Lindholm K, Linnell FS. Invasive lobular carcinoma: mammographic findings in a 10-year experience. Radiology 1991;178:149-54.
48. White JR, Gustavson GS, Wimbish K, Ingold JA, Lucas RJ, Levine AJetal - Conservative surgery and radiation therapy for infiltrating lobular carcinoma of the breast. The role of preoperative mammograms inguiduing treatment. Cancer 1994;74:640-7
49. Paramagul CP, Helvie MA, Adler DD. - Invasive lobular carcinoma: sonographic appearance and role of sonography in improving Diagnostic sensitivity. Radiology 1995; 195:231–234.
50. Le Gal M, Ollivier L, Asselain B, et al. Mammographic features of 455invasive lobular carcinomas. Radiology 1992; 185:705–708
51. Hilleren DJ, Andersson IT, Lindholm K, Linnell FS. Invasive lobular carcinoma: mammographic findings in a 10-year experience. Radiology 1991;178: 149–154.
52. Gisvold JJ. Imaging of the breast: techniques and results. Mayo Clin Proc1990; 65:56–66
53. Porter AJ, Evans EB, Foxcroft LM, Simpson PT, Lakhani SR. Mammographic and ultrasound features of invasive lobular carcinoma of the breast. J Med Imaging Radiat Oncol. 2014;58(1):1-10
54. Evans WP, Warren Burhenne L, Laurie L et al. Invasive lobular carcinomaof the breast: mammographic characteristics and computer aided detection. Radiology 2002;225:182-9
55. Michael, M., Garzoli, E., et Reiner, C. S. Mammography, sonography andMRI for detection and characterization of invasive lobular carcinoma of the breast. Breast disease, 2008, vol. 30, no 1, p. 21-30
56. Travade, Armelle, Alain Isnard, and Henry Gimbergues. Imagerie de lapathologie mammaire. Masson, 1996
57. Uchiyama, Nachiko, et al. "Radiographic features of invasive lobularcarcinoma of the breast. " Radiation medicine 19.1 (2001) : 19.
58. Weinstein S, Greenstein Orel S, Reynolds C et al. MR imaging of the breastin patients with invasive lobular carcinoma. AJR 2001;176 : 339-406
59. Albayrak, Zeynep Kırkalı, et al."Invasive lobular carcinoma of the breast:mammographic and sonographic evaluation." Diagn Interv Radiol 17.3(2011): 232-238
60. Butler RS, Venta LA, Wiley EL, Ellis RL, Dempsey PJ, Rubin E. Sonographic evaluation of infiltrating lobular carcinoma. Am J Roentgenol. 1999;172(2):325 30
61.Selinko VL, Middleton LP, Dempsey PJ. Role of sonography In diagnosing and staging invasive lobular carcinoma. J Clin Ultrasound. 2004;32(7):323-3
62. Michele L., Liliane O., Dernard A., Martine M., Michel L., Philippe V., Sylvia N. Mammographic featues of 455 invasive lobular carcinomas Raddiology1992 :705-708
63. Escolano E., Finck B., Allouch J.M., Bernard P., Racinet C. Interet de l'échographie Doppler couleur dans l'éxploration des tumeurs du sein J. Gynécol. Obstet. Biol. Reprod. 1992 :87
64. Francesco Sardanelli et al - Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group .2010.02.015
65. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005;23:8469–76.
66. Sardanelli F, Podo F, D'Agnolo G, et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): Interim results. Radiology 2007;242:698–715
67.Qayyum A, Birdwell R, Daniel BL et al. MR imaging of infiltrating lobular carcinoma of the breast: histopathologic correlation. AJR 2002; 178:1227-32
68. McGhan LJ, Wasif N, Gray RJ, Giurescu ME, Pizzitola VJ, Lorans R, et al. Use of Preoperative Magnetic Resonance Imaging for Invasive Lobular Cancer: Good, Better, but maybe not the Best? Annals of Surgical Oncology. 2010 Oct;17(S3):255–62.
69. Roxane Gest a,b, Sophie Cayet b,c, Flavie Arbion d, Anne Vildé - Predictive factors of concordance (5mm threshold) between MRI and histological sizes of invasive lobular breast cancer 2019 Mar;47(3):291-296
70. C. Balleyguier, C. Dromain* Input of new imaging modalities for breast cancer staging N° 73 - 2016*
71. Dromain C, Thibault F, Muller S, Rimareix F, Delaloge S, Tardivon A et al.Dual-energy contrast-enhanced digital mammography: initial clinical results. Eur Radiol 2011;21(3):565-74.
72. Pascal Chérel, Les biopsies mammaires : indications et critères de qualité/ J Radiol 2005 ; 86:1228-1453
73. Liberman L, LaTrenta LR, Denhaw DD, Abratnson AF, Morris EA, Cohen MA et nl. Impact of core biopsy on the surgical management of impalpable breast cancer. AJR 1997 ; 168:495-9
74. Yitn JH, Barton P, Weber B, Radford D, Levy J, Monsees B et al. Mammographically detected breast cancer: benefits if stereotactic core versus wire localization biopsy. Ann Surg 1996; 223:688-700.
75. Smith RN, Christian R, Meyer JE. Large core needle biopsy of non-palpable breast cancers: the impact on subsequent surgical excision. Arch Surg 1997; 132 :256-9.
76. Chopier, J., Antoine, M., Duffaut, C., et al. - Lésions infra cliniques mammaires : corrélations radio-pathologiques sur les pièces d'exérèse chirurgicale. Intérêt pour le choix des techniques d'exérèse a minima. Gynécologie obstétrique & fertilité, 2000, vol. 28, no 12, p. 888-895

77. CHAN A, PINTILIE M, VALLIS K, GIROURD C, GOSS P. - Breast cancer in women ≤35 years: review of 1002 cases from a single institution. Ann Oncol 2000;11:1255 62
78. Fondriner E, Guérin O, Lorimier G. Etude comparative de l'évolution métastatique des carcinomes canalaires et lobulaires du sein à partir de deux séries appariées (376 patientes). Bull cancer. 1997; 84(12):1101-7
79. www.oncolor.org ESMO 2002
80. BALU-MAESTRO.C, CHAPELLIER.C, DARCOURT.J, ETTORE.F, RAOUST.I - Imagerie dans le bilan d'extension ganglionnaire et métastatique du cancer dusein. Journal de radiologie (Paris) vol186 (11) 2005 : p1649-1657
81. MoïseNamer, Daniel Serin, Marc Spielmann - Cancer du sein : Compte-rendu du cours supérieur francophone de cancérologie, édition 2007
82. Raudrant D., Golfier F., Unger P.Le traitement des carcinomes in situ du sein. Rev. Fr. Gynécol. Obstet., 1990 : 92,94,95
83 .Clere, N. (2016). Les traitements du cancer du sein. Actualités Pharmaceutiques, 55(558), 20–25.
84. M.G. Berry et al. Oncoplastic breast surgery: a review and systematic approach J Plast Reconstr Aesthet Surg (2010)
85. Demange L., Nzengu B., Rigaud C. Tumoréctomie limitée associée a la curithérapie per-opératoire pour le traitement consérvateur du cancer du sein. J.Gynécol. Obstet. Biol. Reprod. 1992 : 479-482

86. Nicolas Daly-Schveitzer - Cancérologie clinique 2008.GG SENTINELLE
87. J. Saglier. - Le cancer du sein non métastatique. Mise au point. J Chir2005,142, N°6
88. V.Doriot. C., Nnos.J.S., Aucoutruer. Le traitement chirurgical conservateur du cancer du sein. Cancer/radiothérapie 8 (2004) : 21-28
89. Demange L., Nzengu B., Rigaud C. Tumorectomie limitée associée a la curithérapie per-opératoire pour le Traitement consérvateur du cancer du sein. J.Gynécol. Obstet. Biol. Reprod. 1992 : 479-482
90. Newman LA. Current issues in the surgical management of breast cancer: areview of abstracts from the 2002 San Antonio Breast Cancer Symposium, Society of Surgical Oncology annual meeting, and the American Society ofClinical Oncology meeting. Breast J 2004; 10 Suppl 1:S22-S25
91. Houvenaeghel, G., Lambaudie, E., Buttarelli, M., et al. - Marge d'exérèsedans les cancers infiltrants du sein. Bulletin du Cancer, 2008, vol. 95, no 12,p. 1161-1170.
92. Nos C., Fitoussi A., Bourgeois D., Clough KB. La chirurgie du creuxaxillaire en 1998. Cancer/Radiothérapie, 1998, 2 (5) : 475-481
93. B. Oliviera, J.-L. Verhaeghea, M. Butarellib, F. Marchala, G.Houvenaeghel. - Anatomie fonctionnelle du drainage lymphatique du sein : apport de la technique du lymphonoeud sentinelle. Annales de chirurgie 131(2006) 608–615
94. Delay E, Ho Quoc C, Garson S, Toussoun G, Sinna R. - Reconstruction mammaire autologue par lambeau musculocutanéo-graisseux de grand dorsal pédiculé. EMC Techniques chirurgicales — Chirurgie plastique reconstructrice et esthétique 2010 [45-665-C]
95. Ho Quoc C, Bouguila J, Brun A, Voulliaume D, Comparin JP, Foyatier JL. - Traitement chirurgical des séquelles de brûlures profondes du sein : 25 ans d'expérience. Ann Chir Plast Esthet 2012;57:35—40
96. Delay E, Delaporte T, Sinna R. - Alternatives aux prothèses mammaires. Ann Chir Plast Esthet 2005; 50:652—72
97. Blondeel PN. - One hundred free DIEP flap breast reconstructions: a personal experience. Br J Plast Surg 1999;52: 104—11
98. Allen RJ, Tucker C. - Superior gluteal artery perforator free flap for breast reconstruction. Plast Reconstr Surg 1995;95: 1207—12.
99. Ho Quoc, C., & Delay, E. (2013) - Reconstruction mammaire après mastectomie. Journal de Gynécologie Obstétrique et Biologie de La Reproduction, 42(1), 29–39.
100. B. Cutuli. - Radiothérapie des cancers du sein en 2012 : quelles stratégies ? Cancer/Radiothérapie 16 (2012) 493–502.
101. Early Breast Cancer Trialist Collaborative Group (EBCTCG) - Effect ofradiotherapy after breast conserving surgery on 10-year recurrence and 15-year breast cancer death: metat-analysis of individual patient data for 10801women in 17 randomized trials. Lancet 2011;378:771–84
102. Whelan TJ, Pignol JP, Levine MN, Julian JA, Mackenzie R, Parpia S - Long term results of hypofractionated radiation therapy for breast cancer. N Engl JMed 2010; 362:513–20
103. Hennequin, C., Barillot, I., Azria, D., Belkacémi, Y., Bollet, M., Chauvet, B., Mahé, M. A. (2016). Radiothérapie du cancer du sein. Cancer/Radiothérapie, 20, S139–S146.
104. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013; 31:2382–7
105. S. HELFRE, C. GINESTET et C. CARRIETechniques d'irradiation du cancer du sein et de ses métastases. Encycl. Méd. Chir. (Elsevier, Paris); 871-A-30, 1996, 5p.
106. Jacquillat C, Weil M, Baillet F et al. (1990) Results of neoadjuvant chemotherapy and radiation therapy in the breast-conserving treatment of 250 patients with all stages of infiltrative breast cancer. Cancer 66:119-29

107. Chevallier B, Chollet P, Merrouche Yet al. (1993)
Lenograstim prevents morbidity from intensive induction chemotherapy in the treatment of inflammatory breast cancer. J Clin Oncol 13:1564-71
108. Bonadonna G, Valagussa R Brambilla C et al. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. J Clin Oncol 16: 93- 100
109. Gonçalves A.Chimiothérapie néo-adjuvante des cancers du sein HER2-positifs et triple-négatifs. Bull. Cancer (Paris) 2016; 103:S76–S89.
110. Early Breast Cancer Trialists'Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687-717
111. Early Breast Cancer Trialists'collaborative Group (1992) Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 339: 1-15, 71-85 48.

112. Early Breast Cancer Trialists'Collaborative Group (1998)- Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 352:930-42
113. Roche.H - Traitements médicaux du cancer du sein. La revue du praticien (Paris).54 (2004) : 855-864
114. Roche H, Fumoleau P, Spielmann M Et Al. - Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol 2006 ; 24:5664-71
115. Fumoleau P, et al. - Randomized trial comparing six versus three cycles of epirubicin-based adjuvant chemotherapy in premenopausal, node-positivebreast cancer patients: 10-year follow-up results of the French AdjuvantStudy Group 01 trial. J Clin Oncol 2003; 21:298—305.
116. S. Aebi1, T. Davidson, G. Gruber F. Cardoso. - On behalf of the ESMOGuidelines Working Group Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Clinical practice guidelines. Annals of Oncology 22 (Supplement 6): vi12–vi24, 2011.
117. Saltel-Fulero A, Donnadieu A, Leman-Detours S, Cottu P. - Nouvelles options en hormonothérapie adjuvante des cancers du sein. Bull. Cancer (Paris) 2016 ; 103:104–112
118. AGRUP, STAL O, OLSEN K, WINGREN S. C-erb-2 Overexpression and survival in early onset breast cancer. Breast cancer Res Treat 2000,63(1) :23-29
119. Jannuzzo MG, Di SE, Spinelli R, Pirotta N, Buchan P, Bello - A. Estrogen suppression in premenopausal women following 8 weeks of treatment with exemestane and triptorelin versus triptorelin alone. Breast Cancer Res Treat 2009;113:491—9.
120. De Cremoux, P. (2011). - Hormonothérapie des cancers du sein. Bulletin Du Cancer, 98(11), 1311–1319.
121. Référentiel diagnostique et thérapeutique SEIN – SENORIF 2021-2023 - CANCERS ET PATHOLOGIES DU SEIN ATTITUDES DIAGNOSTIQUES ET THERAPEUTIQUES, PROTOCOLES DE TRAITEMENT 2021-2022
122. Coussy, F., Teixeira, L., Giacchetti, S., Cuvier, C., Hocini, H., & Espié, M. (2014).- Nouveautés sur les thérapies ciblées dans le cancer du sein. Gynécologie Obstétrique & Fertilité, 42(11), 787–794.
123. Janiszewska M, Liu L, Almendro V, Kuang Y, Paweletz C, Weigelt B, et al.
Abstract PR05: The effect of chemotherapy on HER2+ breast cancer heterogeneity measured by STAR-FISH: Detection of PIK3CA mutation and HER2 amplification at single-cell level in situ.AACR; 2016
124. TUMA RS. Trastuzumab trials steal show at ASCO meeting. J Natl CancerInst 2005;97:870–1. 202.
125. M. NAMER, J. GLIGOROV, E. LUPORSI, D. SERIR.Cancers du sein: Recommandations pour la pratique clinique de saint-Paul -de -Vence. Oncologie; 2005, 7, pp : 345-352
126. aniszewska M, Liu L, Almendro V, Kuang Y, Paweletz C, Weigelt B, et al.
Abstract PR05: The effect of chemotherapy on HER2+ breast cancer heterogeneity measured by STAR-FISH: Detection of PIK3CA mutation and HER2 amplification at single-cell level in situ. AACR; 2016
127. M. Hussien, T.F. Lioe, J.
Finnegan and R.A. Spence, Surgical treatment for invasive lobular carcinoma of the breast, Breast 12 (2003), 23–35.
128. http://www.centre-des-coteaux.be/site.php?r=comprendre le cancer du sein
129. Classe JM, Loussouarn D, Campion L.Validation of axillary sentinel lymph node detection in the staging of early lobular invasive breast carcinoma: a prospective study. Cancer 2004; 2004(100):5
130. M.A. Chung, B. Cole, H.J. Wanebo, K.I. Bland and H.R. Chang, Optimal surgical treatment of invasive lobular carcinoma of the breast, Ann Surg Oncol 4 (1997), 545–550. 207.
140. S.E. Singletary, L.Patel-Parekh and K.I. Bland, Treatment trends in early stage invasive lobular carcinoma: a report from the National Cancer Data Base, Ann Surg 242 (2005), 281–289
141. Du Toit RS, Cocker AP, Ellis IO, Elston CW, Nicholson RL, Robertson JFR& Blamey RW 1991
An evaluation of differences in prognosis, recurrencepatterns and receptor status between invasive lobular and other invasive carcinomas of the breast. European Journal of Surgical Oncology 17 251 257.
142. Classe JM, Loussouarn D, Campion L. Validation of axillary sentinel lymphnode detection in the staging of early lobular invasive breast carcinoma: a prospective study. Cancer 2004; 2004(100): 5

143. EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–717
144. Paramagul CP, Helvie MA, Adler DD.
Invasive lobular carcinoma: sonographic appearance and role of sonography in improving diagnostic sensitivity. Radiology 1995; 195:231–234.
145. Skaane P, Skjorten F. Ultrasonographic evaluation of invasive lobularcarcinoma. Acta Radiol 1999;40:369–75
146. Cristofanilli M, Gonzalez-Angulo A, Sneige N, Kau SW, Broglio K, Theriault RL, et al.
Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. J Clin Oncol 2005;23(1):41—8

147. Marinovich ML, Macaskill P, Irwig L, Sardanelli F, Mamounas E, von Minckwitz G, et al. Agreement between MRI and pathologic breast tumor size after neoadjuvant chemotherapy, and comparison with alternative tests: individual patient data meta-analysis. BMC Cancer 2015; 15: 662.
148. Vriens IJH, Keymeulen K, Lobbes MBI, van Bommel ACM, Nieuwenhuijzen GAP, Smidt ML, et al.
Breast magnetic resonance resonance imaging use in patients undergoing neoadjuvant chemotherapy is associated with less mastectomies in large ductal cancers but not in lobular cancers. Eur J Cancer 2017;81: 74—80
149. MATHIEU, M.-C., ROUZIER, R., LLOMBART-CUSSAC, A., et al. The poor responsiveness of infiltrating lobular breast carcinomas to neoadjuvant chemotherapy can be explained by their biological profile. European Journal of Cancer, 2004, vol. 40, no 3, p. 342-351
150. Braud AC, Asselain B, Scholl S, et al.
Neoadjuvant chemotherapy in young breast cancer patients: correlation between response and relapse EurJCancer 1999, 35, 392–397.
151. Pelissier P, Delaloge S, Mathieu MC, et al.
Intensified anthracyclin doses donot improve clinical and pathological responses to neoadjuvant FEC for operable breast cancer: results of a multicenter randomised trial. Proc Am SocClinOncol 2002, 21, 64a
152. Sikora, Matthew J., Jankowitz, Rachel C., Dabbs, David J., et al.
Invasivelobular carcinoma of the breast: patient response to systemic endocrine therapy and hormone response in model systems. Steroids, 2012
153. Lorfida M, Maiorano E, Orvieto E, Maisonneuve P, Bottiglieri L, RotmenszN, et al.
Invasive lobular breast cancer: subtypes and outcome. Breast Cancer Res Treat 2012;133:713–23.
154. Smith DB, Howell A, Wagstaff J. - Infiltrating lobular carcinoma of thebreast: response to endocrine therapy and survival. Eur J Cancer Clin Oncol1987 ; 23:979–82
155. Rakha EA, El-Sayed ME, Powe DG, Green AR, Habashy H, Grainge MJ, etal.
Invasive lobular carcinoma of the breast: response to hormonal therapy and outcomes. Eur J Cancer 2008;44:73–83
156. Sikora, Matthew J., Jankowitz, Rachel C., Dabbs, David J., et al.
Invasive lobular carcinoma of the breast: patient response to systemic endocrine therapy and hormone response in model systems. Steroids, 2012.
157. Reis-Filho, Jorge Sergio, Simpson, Pete T., Turner, Nicholas C., etal.
FGFR1 emerges as a potential therapeutic target for lobular breast carcinomas. Clinical Cancer Research, 2006, vol. 12, no 22, p. 6652-6662
158. Maggard, J.B. O'Connell and K.E. Lane.
Do young breast cancer patients have worse outcomes? J Surg Res, 2003; 113 : 109–13.
159. Yeatman TJ, Cantor AB, Smith TJ.
Tumor biology of infiltrating lobularcarcinoma. Implications for management. Ann Surg 1995;222(4):549–61
160. Toikkannen S, Phylkkannen L, Joennsuu H.
Lobular carcinoma of the breasthas better short term and long-term survival than ductal carcinoma. Br J Cancer 1997; 76(9) : 123
161. Dixon AR, Ellis IO, Elston CW, Blamey RW.
A comparison of the clinicalmetastatic patterns of invasive lobular and ductal carcinomas of the breast. Br J Cancer 1991 ; 63 : 634-635.
162. Casolo P, Raspadori A, Drei B, Amuso D, Mosca D, AMOROTTI C, DIBLASIO P, DE MARIA R.
Natural history of breast cancer : lobular carcinoma of the breast versus ductal carcinoma in our experience. Ann Ital Chir 1997 ; 69(1) : 43-48
163. Orvieto E, Maiorano E, Bottiglieri L, Maisonneuve P, Rotmensz N, Galimberti V, Luini A, Brenelli F, Gatti G, Viale G,
Clinicopathologic characteristics of invasive lobular carcinoma of the breast: results of an analysis of 530 cases from a single institution, Cancer, 2008, 113(7):1511– 1520.

164. Silver SA, Tavassoli FA,
Pleomorphic carcinoma of the breast: clinicopathological analysis of 26 cases of an unusual high-grade phenotype of ductal carcinoma, Histopathology, 2000, 36(6):505–514.
165. du Toit RS, Locker AP, Ellis IO, Elston CW, Nicholson RI, Blamey RW,
Invasive lobular carcinomas of the breast – the prognosis of histopathological subtypes,
Br J Cancer, 1989, 60(4):605–609.
166. Lorfida M, Maiorano E, Orvieto E, Maisonneuve P, Bottiglieri L, Rotmensz
N, et al. Invasive lobular breast cancer: subtypes and outcome. Breast Cancer Res Treat 2012;133:713–23
167. Frolik D, Caduff R, Varga Z,
Pleomorphic lobular carcinoma of the breast: its cell kinetics, expression of oncogenes and tumour suppressor genes compared with invasive ductal carcinomas and classical infiltrating lobular carcinomas, Histopathology, 2001, 39(5):503–513.
168. Middleton LP, Palacios DM, Bryant BR, Krebs P, Otis CN, Merino MJ,
Pleomorphic lobular carcinoma: morphology, immunohistochemistry, and molecular analysis, Am J Surg Pathol, 2000, 24(12):1650–1656
169. Porter, A. et al.
Patterns of metastatic breast carcinoma: influence of tumour histological grade. Clin Radiol, 2004; 59(12) : 1094-8
170. Buchanan CL, Flynn LW, Murray MP, Darvishian F, Cranor ML, Fey JV,King TA, Tan LK,
Sclafani LM,
Is pleomorphic lobular carcinoma really a distinct clinical entity J Surg Oncol, 2008, 98(5):314–317
171. M.L. Talman, M.B. Jensen and F.
Rank, Invasive lobular breast cancer. Prognostic significance of histological malignancy grading, Acta Oncol 46(6) (2007), 803–809.
172. Galant, Christine, Berlière, M., Leconte, Isabelle, et al.
Nouveautés dans lesfacteurs histopronostiques des cancers du sein. Imagerie de la Femme, 2010, vol. 20, no 1, p. 9-17.
173. Quiet CA, Ferguson DJ, Weichselbaum RR, Hellman S.
Natural history ofnode-positive breast cancer: the curability of small cancers with a limited number of positive nodes. J Clin Oncol 1996;14:3105—11
174. MacGrogan G, Jollet I, Huet S, Sierankowski G, Picot V, Bonichon F,Coindre JM:
Comparison of quantitative and semiquantitative methods of assessing MIB-1 with the S-phase fraction in breast carcinoma.Mod Pathol 1997, 10:769-776
175. Philippidou, Marianna et Pinder, Sarah E.
Invasive Lobular Carcinoma ofthe Breast. Surgical Pathology Clinics, 2012, vol. 5, no 3, p. 545-566.
176. Lee, Ju-Hyun, Park, Seho, Park, Hyung Seok, et al.
Research Clinicopathological features of infiltrating lobular carcinomas comparing with infiltrating ductal carcinomas: a case control study. 2010
177. Galant, Christine, Berlière, M., Leconte, Isabelle, et al.
Nouveautés dans les facteurs histopronostiques des cancers du sein. Imagerie de la Femme, 2010, vol. 20, no 1, p. 9-17
178. J Kollias, CW Elston, 10 Ellis, JFR Robertson and RW Blamey Early-onset
Breast cancer : histopathological and prognostic considerations. British Joumal of Cancer (1997) 75(9), 1318-1323.
179. Azria, C. et al.
Hormonoradiothérapie adjuvante concomitante des cancers du sein: état de l'art Cancer/Radiothérapie 2004 ; 8 (3) : 188-96
180. Coradini D, Pellizzaro C, Veneroni S, Ventura L & Daidone MG 2002
Infiltrating ductal and lobular breast carcinomas are characterised by different interrelationships among markers related to angiogenesis and hormone dependence. British Journal of Cancer 87 1105–1111
181. Scholl S, Beuzeboc P, Pouillart P.
Targeting Her2 in other tumor types. Annals of Oncology 2001;(suppl.1):S81–7.
182. Varga Et Al.
Preferential HER-2/neu overexpression and/or amplification inaggressive histological subtypes of invasive breast cancer, Histopathology 44(4) (2004), 332–338
183. VARGA, Zsuzsanna et MALLON, Elizabeth.
Histology andimmunophenotype of invasive lobular breast cancer.Daily practice and pitfalls. Breast disease, 2008, vol. 30, no 1, p. 15-19
184. G. Acs et al.
Differential expression of E-cadherin in lobular and ductalneoplasms of the breast and its biologic and diagnostic implications, Am J Clin Pathol 115(1) (2001), 85–98.
185. I.T.Yeh and C. Mies,
Application of immunohistochemistry to breastlesions, Arch Pathol Lab Med 132(3) (2008), 349–358.

186. B.J. Yoder, E.J. Wilkinson and N.A. Massoll,
Molecular and morphologicdistinctions between infiltrating ductal and lobular carcinoma of the breast, Breast J 13(2) (2007), 172–179
187. Moreno-Elola, A., Roman, J. M., Aguilar, A., et al.
Survie du carcinomelobulaire invasif du sein: Impact du stade tumoral sur le pronostic. le Sein, 1999, vol. 9, no 3, p. 177-182
188. Cutuli B, Prevot G, Parache RM, et al
Cancer lobulaire infiltrant :résultat après traitement conservateur. XVIe Journées nationales de la société française de sénologie et de pathologie mammaire, Dijon, Octobre Abstract book, 34–5
189. PICCART, Martine, DOCHY, Emmanuelle, et CARDOSO, Fatima.
Actualités thérapeutiques dans le traitement médical du cancer dusein. Bulletin du cancer, 2003, vol. 90, no 1, p. 46-52
190. Warneke J, Berger R, Johnson C, Stea D & Villar H 1996
Lumpectomy andradiation treatment for invasive lobular carcinoma of the breast.AmericanJournal of Surgery 172 496–500.
191. Sariego J, Byrd M, Kerstein M, Matsumoto T.
Factors influencing survivalin infiltrating lobular carcinoma of the breast. The American Surgeon 1993; 59: 405-109
192. Brouckaert, O., Laenen, A., Wildiers, H., Et Al.
Prognostic Implicationsof Invasive Lobular Breast Cancer.European Journal of Cancer, 2012, vol. 48, p. S142. Endocrine-related cancer, 2007, vol. 14, no 3, p. 549-567
193. Petrausch, U. et Pestalozzi, B. C.
Distinct Clinical and Prognostic Featuresof Invasive Lobular Breast Cancer.Breast disease,
2008, vol. 30, no 1, p. 39-44