Clinico-pathological Characteristics of Invasive Lobular Carcinoma of the Breast

By

Changkel Banak Riak Dong

M.B.B.S. (University of Juba, 1997)

A thesis submitted in partial fulfillment for the requirements of the degree of Clinical MD in Pathology, 2010

Supervisor

Dr. Mohamed M. Osman

(MD, U of K)

2010
## TABLE OF CONTENTS

| Dedication | i |
| Acknowledgement | ii |
| Abstract (English) | iii |
| Abstract (Arabic) | iv |
| List of Abbreviations | v |

### CHAPTER ONE

1. Introduction and literature review  
   1.1 Anatomy and Pathology of the breast  
   1.2 Invasive Breast Carcinomas  
   1.3 Other Histological and Clinical Types  
   1.4 Microscopic Pathology for Invasive Breast Carcinoma  
   1.5 Prognostic Factors of Invasive Breast Carcinoma  
   1.6 Additional Prognostic Markers by Immunochemistry & Flow cytometry  
   1.7 Clinicopathologic characteristic of invasive lobular Carcinoma of the Breast  
   1.8 Gross Pathology for Invasive Lobular Carcinoma  
   1.9 General Histological Features for Invasive Lobular Carcinoma  
   1.10 Special Subtypes of Invasive Lobular Carcinoma  
   1.11 Grading of Invasive Lobular Carcinoma  

Page No.

1  
2  
3  
8  
11  
14  
15  
19  
21  
22  
23  
25
1.12 Differential Diagnosis for Invasive lobular Carcinoma  26
1.13 Immunohistochemistry  29
1.14 Prognosis for invasive Lobular Carcinoma  32
Objectives  34

CHAPTER TWO

2. Materials and Methods  35

CHAPTER THREE

3. Results  39

CHAPTER FOUR

4.1 Discussion  55
4.2 Conclusions  60
4.3 Recommendations  61
References  62
Appendix  65
DEDICATION

To:

my grandfather, Sultan late “Riak Dong”

my father, late “Joseph” “Kauclieth”

my mother “Sabina”.

my family “Agum & Kamdan”

all friends,

with love.
ACKNOWLEDGMENT

I would like to extend my sincere appreciation to National Health Laboratory, the histopathology department staff and all who helped in preparation, data collection and slide sections production.

This job could not been possible without the guidance, knowledge and wisdom of Prof. Bashir I. Mukhtar and Dr. Mohamed M. Osman, who guide me diligently, and without their knowledge and professionalism, this work, will never see light.

I am greatly indebted to those gentlemen who supported me and led me all the way to a successful completion.

I wish to thank the Khartoum State Laboratories Administration, the histopathology department for their continuous support and, contribution, above that allowing me to use their laboratory facilities.

Finally I wish to thank my family, my wife Agum and daughter Kamdan for the support and encouragement over yet another demand on time that could have been spent with them.
ABSTRACT

Introduction: Knowledge about the biological, clinical and pathological characteristics of invasive lobular carcinoma of breast has remained complex and unclear due to rarity of such cases.

Objectives: This is a retrospective study to highlight the clincopathological features of invasive lobular carcinoma; and to identify the incidence rate among the invasive breast cancers.

Methods: Clinical and histological data from archived and reported 508 cases diagnosed as invasive breast cancers, from period 2005 – 2009 at National Health Laboratory were collected and reviewed. Among 508 cases, 30 patients reported as invasive lobular carcinoma of the breast were studied by recutting new section and histopathologically assessed and immunohistochemical reactivity for ER and PR done on paraffin embedded blocks of the 30 cases of ILC.

Results: The incidence rate of invasive lobular carcinoma was 5.9%. The average age of the patients was 57.5 years (range, 30- 85 years), and 60% (18) were in postmenopausal age. Most of the tumours were classical ILC grade 2 in 73.3% of cases. The other lymph nodes were positive in 40% and negative in 60% with ILC. The proportion of estrogen and progesterone receptors positive tumours were 21(70%) cases and 15(50%) cases respectively.

Conclusions: The incidence rate of ILC was increasing as well as other invasive breast carcinomas. ILC is more likely to occur in older age. The lymph node metastasis tends to be lower in ILC than in other invasive breast carcinomas. The ER and PR reactivity is more frequently positive with ILC.
من مقدمة:

البيئة وخصائص الغازية الفصصية للسرطان والمرضية والسيرية اللوجية السبب وقصد ووضوح وغير معقدة الأ حالات مثل الندرة ب.

الأهداف:

الخصائص بعض العلى الضوء التسليط التي تنقد الأواء بالدراسة هذه الأنواع بين النزعة الغازية الفصصية السرطانية حدوث معدل معرفة التي وبدلاً واضحة وباضحة وتجري وقائد توجيه وانعقاد في.

البحث منهجية:

بيانات جمع تم 508 حالة الفيروسية في الحالة القزحي بين 2005 و 2009 وبدلاً بالموارد والنسجية السيرية الفحص ببعد التشخيص واتخاذ والتي تصرف таблиц والمناعية الفحص وإجراء النظير لهذه وابتسامات والبرجسترن الإسترن الحرمونية الكيميائية النسجية.

النتائج:

الغازية الفصصية بالسرطان الاصابة حدوث معدل 5.9% وعدد哒رات بين 30 و 65 سنة (عند الأكبر حدد) 73.3% في نسبة من البالغ بإضافة حالة من السرطانية الفحصية 40% وسلبية في 60% الحالات ونسبة الأملية 70% (لا يعرف الناحية) كشف الكيمائي كنابذة غير تعليل توني في يدالو في لندغة تنقاة والتراكيز في ت يเสมط واعدة وانطلاق.

التزداد أنواع 65.0% وهو لامترن الناحية يكذب في واتساج يقل بحالة وفار ودة. لذا الطبيب الفيزيائي كتبت بوضع النزعة صعبة ي metod ليداز نشاط بالوصف و لدى ناهز لينجرnes الذي في كف العديل الطبي.t شوقت تجربة تعليل.
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>Ductal Carcinoma In-Situ</td>
</tr>
<tr>
<td>EIC</td>
<td>Extensive Intraductal Component</td>
</tr>
<tr>
<td>ER</td>
<td>Estrogen Receptor</td>
</tr>
<tr>
<td>GCDPF</td>
<td>Gross Cystic Disease fluid protein</td>
</tr>
<tr>
<td>IDC</td>
<td>Invasive Ductal Carcinoma</td>
</tr>
<tr>
<td>ILC</td>
<td>Invasive Lobular Carcinoma</td>
</tr>
<tr>
<td>LCIS</td>
<td>Lobular Carcinoma In-Situ</td>
</tr>
<tr>
<td>NOS</td>
<td>Not Otherwise Specified</td>
</tr>
<tr>
<td>NR</td>
<td>Not Recommended</td>
</tr>
<tr>
<td>PR</td>
<td>Progesterone Receptor</td>
</tr>
<tr>
<td>R</td>
<td>Recommended</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance Epidemiology and End Results</td>
</tr>
<tr>
<td>TDLU</td>
<td>Terminal Duct-Lobular Unit</td>
</tr>
</tbody>
</table>


1. INTRODUCTION AND LITERATURE REVIEW

Knowledge about the biological, clinical and pathological characteristics of invasive lobular breast carcinoma of the breast is complex and unclear.

Invasive lobular carcinoma of the breast (ILC) comprises approximately 5-10% of all invasive breast cancer.\(^{(6)}\) A precise histological and clinical delineation of invasive lobular carcinoma, including its variants form, has been elusive.\(^{(11)}\)

Invasive lobular breast carcinoma (ILC) displays diverse histological pattern varying from classical variant through solid to pleomorphic subtypes.\(^{(4)}\)

These tumours are characterized microscopically by small cells that insidiously infiltrate the mammary stroma and adipose tissue individually and in single file pattern, often forming target -like configuration around normal breast ducts, frequently inducing only minimal fibrous reaction.\(^{(3)}\)

By virtue of their distinctive growth pattern and biology, lobular carcinomas often fail to form distinct masses that can easily be diagnosed by palpation or mammography. This can make early diagnosis challenging and breast conservation approaches more difficult.\(^{(6)}\)

Lobular carcinomas may have a substantially increased propensity for multifocal and mutlicentric distribution and bilaterality. Invasive lobular
carcinoma frequently metastasized to unusual sites, including the gastrointestinal tract, peritoneum, and adnexa.\(^{(6, 16)}\)

The majority of invasive lobular breast carcinomas (ILC) show strong expression of estrogen and progesterone receptors, a higher rate than other invasive carcinomas.\(^{(4)}\)

Previously invasive lobular carcinoma (ILC) was considered to be an aggressive tumour, but later on it was shown to have fairly favorable prognosis. However, some histological subtypes (i.e pleomorphic) have much worse prognosis.\(^{(16)}\)

1.1. Anatomy and pathology of the breast:

The breast or mammary gland is covered by skin and subcutaneous tissue and rests on the pectoralis muscle, from which it is separated by a fascia. The morpho-functional unit of the organ is single gland, a complex branching structure that is composed of two major parts: the terminal duct-lobular unit (TDLU) and the large duct system.\(^{(1)}\)

The breast is composed of glandular ducts and lobules, connective tissue and fat. The ductal-lobular unit (TDLU) is the basic structural unit of the breast and is lined by epithelial cells. Specifically, most breast cancer is thought to originate in the terminal ductal lobular unit (TDLU) epithelial cells.\(^{(5)}\) Breast also contains blood and lymphatic vessels. Most lymphatic vessels within the
breast lead to the axillary lymph nodes, some also connect to supra-or infraclavicular, and internal mammary nodes.\(^{(1,14)}\)

1.2. Invasive breast carcinomas:

More than 95% of breast malignancies arise from the breast epithelial elements and therefore they are carcinomas. The term "breast Carcinoma" encompasses a diverse group of lesions which differ in microscopic appearance and biologic behavior. Invasive mammary carcinomas are broadly classified into no special type (ductal) and special type cancer. Invasive lobular carcinoma is a member of latter category representing 5 – 10% of all invasive cancers.\(^{(3,6)}\)

Breast carcinomas can be divided into two major groups:

1- **In situ carcinoma**: The tumor cells remain confined to the duct or lobules and shows no evidence of light microscopic invasion into surrounding stroma.

2- **Invasive carcinomas**: The tumor cells invade the breast stroma’ and have the potential to metastasize and result in death of patient.

The invasive breast carcinomas consist of several histological subtypes; the estimated percentages are from a contemporary population- based of series of 135,157 women with breast cancer reported to the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute between 1992 and 2001 (Seattle, USA):
1- Invasive ductal carcinoma- 76%.
2- Invasive lobular Carcinoma – 8%.
3- Ductal/lobular carcinoma-7%.
4- Mucinous (Colloid) carcinoma- 2.4%.
5- Tubular carcinoma- 1.5%.
6- Medullary Carcinoma- 1.2%.
7- Papillary carcinoma- 1%.

Other subtypes, including metaplastic breast cancer, invasive micropapillary breast cancer, Adenoid Cystic carcinoma, Paget disease of the breast and inflammatory carcinoma, all account for fewer than 5% of cases.\(^{(3)}\)

**Invasive ductal carcinoma:**

Invasive ductal carcinoma is the most common type of invasive breast cancer, accounting for 70-80% of invasive lesions. It is also termed invasive carcinoma of no special type or invasive carcinoma not otherwise specified (NOS).

On gross pathologic evaluation, these lesions are typically hard, gray-white, gritty masses on gross pathologic examination which invade the surrounding tissue in a haphazard fashion to create the characteristic irregular, satellite shape. They are characterized microscopically by cords and nest of tumor cells with varying amount of gland formation and cytological features that range from bland to highly malignant.
The malignant cells induce a fibrous response as they infiltrate the breast parenchyma, and this reaction is, in large part, responsible for clinically and grossly palpable mass, the radiologic density, and solid sonographic characteristics of typical invasive carcinomas.

Invasive ductal carcinomas are divided into three grades based upon a combination of architectural and cytological features, usually assessed utilizing a scoring system based on three parameters:

1- Well-differentiated (grade 1): Well–differentiated tumors have cells that infiltrate the stroma as solid nests of glands. The nuclei are relatively uniform with little or no evidence of mitotic activity.

2- Moderately differentiated (grade 2): Well-differentiated tumors have cells that infiltrate as solid nests with some glandular differentiation. There is some nuclear pleomorphism and moderate mitotic activity.

3- Poorly differentiated (grade 3): Poorly differentiated tumors are composed of solid nest of neoplastic cells without gland formation. There is marked nuclear atypical and considerable mitotic activity.

A variable amount of associated ductal carcinoma in situ (DCIS) is present in most. The extent of DCIS but not lobular carcinoma in situ (LCIS) is an important prognostic factor in patients treated with breast conserving therapy,
in which the surgical goal is complete excision of both intraductal and invasive carcinoma.

**Invasive lobular carcinoma:**

The morphological features of invasive lobular carcinoma, (ILC), classical type are characterized by small, round cells that are bland in appearance and have scant cytoplasm, which infiltrate the stroma in single file and surround benign breast tissue in a targeted manner. Infiltration typically does not destroy anatomic structure or incite a substantial connective tissue response.

**Tubular Carcinoma:**

Tubular carcinomas were relatively infrequent in pre-mammography era, accounting for 2% or less of invasive breast cancers. However, in some series of mammographically screened population the incidence is higher, accounting for 10% to 20% of invasive cancers.

Tubular carcinoma is characterized by the presence of well-formed tubular or glandular structures infiltrating stroma.

1- The tubules tend to be elongated, and many have pointed ends.

2- The cells composing the tubules are cuboidal to columnar and often have apical cytoplasmic protrusion or "snouts".

3- The tumors cells are cytologically low grade.
4- Associated DCIS, typically of low grade type, is present in about three-quarters of the cases.

These lesions have a relatively favorable prognosis compared to infiltrating ductal carcinoma; the natural history is indolent and metastases are rare.

**Mucinous (colloid) carcinoma:**

Mucinous carcinomas account for 1-2% of invasive breast cancers and appear to be more common in older patients. These lesions usually have a soft gelatinous appearance on gross examination, and they tend to be well circumscribed. They are characterized microscopically by nests of tumor cells dispersed in large pools of extracellular mucus.

The cells tend to have uniform, low grade nuclei. Similar to tubular carcinomas, these lesions also represent a prognostically favorable variant of invasive breast carcinoma.

**Medullary carcinoma:**

Medullary carcinoma account for anywhere from 1-10% of invasive breast cancers. However, there is considerable interobserver variability in the diagnosis of this type of breast cancer which is, at least in part, dependent upon the classification system employed.

Medullary carcinomas are well circumscribed on macroscopic examination and are often soft and tan-brown with areas of haemorrhage or necrosis.
Circumscription of the lesion is also evident microscopically. The tumor cells are poorly differentiated (high-grade), grow in a syncytial pattern and have an intense associated lymphoplasmacytic infiltrate, and this tumor is actually quite rare if strict diagnostic criteria are followed.

Medullary and medullary-like carcinomas occur more frequently in younger patients than other types of breast cancer. They are also more frequent in women who inherit mutations of the BRCA-1 gene (10% of breast cancers are medullary in this population, as compared to <1% of non-BRCA-1 gene-related breast cancers). However, the majority of breast cancers in patients with BRCA-1 gene mutations (90%) are not medullary. The prognosis for pure medullary carcinomas appears to be somewhat more favourable than that of infiltrating ductal carcinomas, despite their aggressive histologic appearance.

1.3. Other histological and clinical types:

A number of other histologic types account for the remaining invasive breast cancers. These include invasive micropapillary carcinoma, metaplastic carcinoma, adenoid cystic carcinoma and others. Special types of presentation of breast carcinomas, including paget disease and inflammatory carcinoma and other histologies arising in the breast (lymphomas, sarcoma and phyllodes tumors).
**Micropapillary carcinoma:**

Invasive micropapillary carcinoma is a particularly aggressive form of cancer that has a proclivity for lymph node metastasis even when small in size.

**Metaplastic carcinoma:**

Metaplastic carcinoma is a well circumscribed tumor that consists of various combinations poorly differentiated ductal adenocarcinoma, mesenchymal (sarcomatous) and other epithelial (e.g., squamous cell) components. Whether these tumors have a worse prognosis than ordinary invasive ductal cancers is unclear. Some studies suggest that tumors in which the squamous cell component predominates are aggressive and frequently treatment-refractory when compared to other invasive ductal cancers. However, because metaplastic breast cancer was not officially recognized as a distinct pathologic diagnosis until 2000, knowledge about treatment patterns and outcomes is limited. Despite the perception of a worse prognosis, all metaplastic breast cancers are treated similar to other invasive cancers.

**Adenoid cystic carcinoma:**

The rare adenoid cystic carcinoma of the breast has a distinctive histological pattern that is morphologically identical to adenoid cystic carcinoma found in the salivary glands (and other sites). This tumor tends to be associated with a
favorable prognosis, even when tumor size is large; the reported incidence of axillary metastases in most series is less than 5%.

Histological grading based upon the percentage of solid areas (as is used for salivary gland tumors) has been suggested as being prognostically useful, although other disagree. At least two series in which outcomes were not as favorable in most reports were predominating by patients with higher-grade tumours (i.e., the solid variant).

**Inflammatory carcinoma:**

Inflammatory carcinoma is a distinct form of locally advanced breast cancer that is characterized clinically by erythema, oedema, and warmth of the skin breast. The histologic correlate of the clinical picture is dermal lymphatic invasion by tumour cells. The prognosis of this tumour is poor.

**Paget disease:**

Paget disease is a disorder of nipple and areola, characterized clinically by an eczematiod appearance with crusting, scaling or erosion.

Histologically, there are breast cancer cells within the nipple and areolar epidermis. This lesion is virtually always associated with underlying mammary carcinoma which may be either in situ or invasive.\(^{(2, 3)}\)
**1.4. Microscopic pathology for invasive breast carcinomas:**

**Histologic grade:**

The microscopic architecture (growth patterns) in the majority of infiltrating carcinomas is variable and often mixed, although a particular pattern may predominate. The architecture reflects the degree of differentiation. Tubules, cribriform glands, irregular glands, papillae and acini occur in well-differentiated tumours. Cords are common in intermediate grade of tumours. Solid nests and sheets predominate in poorly-differentiated neoplasms.

The nuclear grade is determined by:

1. Uniformity or irregularity of nuclear size and shape.
2. Chromatin particle size (finely or coarsely granular) and distribution (even or uneven).
3. Nucleoli (size and frequency).

In general, there is a good correlation between the architecture and the nuclear features. Those well-differentiated tumours have predominantly glands and uniform tumour cells with small nuclei, fine chromatin, inconspicuous nucleoli and low mitotic activity. Whereas poorly differentiated tumours have mostly nests and sheets present with large, irregular nuclei, coarse chromatin, prominent nucleoli and high mitotic activity. Moderately differentiated
neoplasms are intermediate between the two groups. Because of the heterogeneity within the same tumour, it would be advantageous to adopt a uniform, reproducible system that correlates with prognosis. The Bloom/Richardson (Elston Modified) grading method is one such system. It combines the architecture and nuclear scores into a final histologic grade. This System is recommended for all invasive carcinomas (Page, et al).

**Bloom/Richardson (Elston modified) grading method:**

<table>
<thead>
<tr>
<th>Tubular Formation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majority of tumour (&gt;75%)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate Degree (10-75%)</td>
<td>2</td>
</tr>
<tr>
<td>Little or none (&lt;10%)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nuclear Pleomorphism</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniform Cells (size is not criterion)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate Increase in Variability</td>
<td>2</td>
</tr>
<tr>
<td>Marked Variation (Often large nucleoli)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mitotic Counts (per 10 high power fields)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-5 mitotic figures)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (6-10 mitotic figures)</td>
<td>2</td>
</tr>
<tr>
<td>High (&gt;11 mitotic figures)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final grade</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I, Well differentiated</td>
<td>3-5 points</td>
</tr>
<tr>
<td>Grade II, Moderately differentiated</td>
<td>6-7 points</td>
</tr>
<tr>
<td>Grade III, Poorly differentiated</td>
<td>8-9 points</td>
</tr>
</tbody>
</table>
**Stromal changes:**

These include desmoplastic reaction with proliferation of newly formed fibroblasts in an edematous, myxomatous or highly collagenized matrix. In the background, elastosis also occurs. The number of lymphocytes, plasma cells and histiocytes is variable.

**Vascular lymphatic space invasion:**

This feature should be carefully evaluated and reported. Shrinkage artefact due to fixation produces an empty space between the tumour nest and fibrous stroma. This space is often mis-interpreted as vascular lymphatic space. A true vascular lymphatic space is lined by clearly recognizable endothelial cells. Invasion is most readily seen in the periphery of the tumour and beyond. Less commonly, the tumour cells invade the blood vessels and perineural spaces. Studies have demonstrated that the presence of vascular lymphatic space invasion increases tumour recurrence. The study of (Rosen et al) further reveals that invasion of the lymphatic, capillaries and blood vessels in tumours up to 2 cm in size with or without lymph node metastases increases death rate, when compared to comparable tumours without such a finding (Rosen PP et al, 1981). Perineural space invasion does not have prognostic significance by itself.
**Invasive ductal carcinoma with extensive intraductal component (EIC):**

Within the infiltrating ductal carcinoma, the intraductal carcinoma may be extensive or completely absent. It is important to assess the amount of intraductal carcinoma. Extensive intraductal component (EIC) positive tumors include the following conditions.

1. Predominantly invasive carcinoma containing DCIS in more than 25% of tumour.

2. Predominantly DCIS with focal invasion and DCIS extend beyond the borders of invasive carcinoma.

When treated by conservative surgery and radiotherapy, these EIC positive tumours are more likely to recur than EIC negative tumours. Based on data from Joint Center for Radiation Therapy, 28% of recurrent invasive ductal carcinomas are EIC positive. Five-year actuarial local recurrence rate is 6% and 24% for EIC negative and positive tumours, respectively.

**1.5. Prognostic factors of invasive breast carcinoma:**

A. Tumour size.

B. Histologic and nuclear grades by Bloom/Richardson (Elston Mod.) Grading Method.

C. Presence of lymphatic space invasion.
D. Surgical margin: When treated by conservative surgery and radiotherapy, the local recurrence rate is 3% when margin is cleared of tumour by more than 1 mm, 2% when margin is cleared by less than 1 mm, 9% when the margin is positive in less than three low power fields, and 28% when the margins is positive in more than three low power fields (Joint Center for radiation therapy).

E. Lymph node status: The lymph node status is one of the most important prognostic indicators. In addition, the number of lymph node involved, less than three or four and more, and the amount of metastasis further influence the survival. Tumour cells enter the lymph node via afferent lymphatics. For this reason, metastasis in the early stage occurs predominantly in the subcapsular region. With growth, tumor cells spread to the surrounding extranodal fibroadipose tissue and blood vessels. Extracapsular spread is reported to adversely affect the outcome.

1.6. Additional prognostic markers by immunochemistry and flow cytometry:

A. Estrogen Receptor (ER), Protein and Progesterone Receptor (PR) Protein:

ER positivity is favorable prognostic indicator; PR positivity alone is a weak favorable prognostic indicator. Patients with ER positive metastatic tumour
receiving endocrine therapy had 60% overall clinical response, and 20% reduction in recurrence/mortality (Early Breast Cancer Trialists' Collaborative Group). When ER and PR are combined, the frequency and response rates are summarized as follows (McGuire, et al):

<table>
<thead>
<tr>
<th>Status</th>
<th>Frequency</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/PR+</td>
<td>58%</td>
<td>77%</td>
</tr>
<tr>
<td>ER+/PR-</td>
<td>23%</td>
<td>27%</td>
</tr>
<tr>
<td>ER-/PR+</td>
<td>4%</td>
<td>46%</td>
</tr>
<tr>
<td>ER-/PR-</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>

ER/PR status has been based on biochemical ligand assay, which requires fresh tissue frozen immediately following excision. ER/PR status can be obtained on formalin embedded tissue sections by immunohistochemical stains using monoclonal antibodies.

There is 80-90% agreement between biochemical ligand assay and immunohistochemical stains for ER/PR. The result of the latter is reported by the percent of positive tumour cells. Immunohistochemical stains for ER/PR have several advantages: precise localization, accurate quantification by visual estimates or by digital imaging technique, possible to perform on routinely processed tissue and archival paraffin block from earlier surgery, workable on cells in effusion or smears obtained by fine needle aspiration. However,
laboratory agreement on the type of antibody to use and scoring method is needed.

B. HER-2/neu Oncogen: HER-2/neu is an oncogen and its protein product is located on the cell surface. It may influence growth factor receptor and promote cellular differentiation, adhesion and motility. It is detected by immunohistochemical stain on tissue section. Amplified or over-expression is seen in 20-30% of breast cancers).

HER-2/neu over-expression is a predictive marker for resistance to adjuvant therapy (cytoxan/methotrexate and tamoxifen).

HER-2/neu is over-expressed in high grade DCIS only, therefore cannot be used to distinguish low grade DCIS from atypical ductal hyperplasia.

C. P-53: Tumour suppressor gene and its protein product is a nuclear transcription factor related to cell cycle regulation and apoptosis. It is detected by immunohistochemical stain on tissue section. Abnormal p53 phenotype in tumour is associated with poor clinical outcome among node negative patients

D. Flow DNA cytometry: By flow cytometry, the DNA ploidy patterns and ploidy levels of the stem cells and their cell cycle kinetics can be determined. Isolated tumour cells are obtained from the solid tumour by
mechanical dispersion or enzyme dissection. Most laboratories currently use tumour tissue embedded in paraffin block. The tumour cells are stained with dye specific for DNA suspended in fluid and passed through the laser beam. The DNA content is plotted in a histogram. Benign tissue in the same specimen is processed similarly to serve as diploid control. The Go/G1 peak represents cells in the resting phase. As cells begin to synthesize DNA, the DNA content is increased (S-phase). At the completion of DNA duplication, G2 and M (mitotic) cells produced a second peak with double amount of DNA.

The ploidy level of stem cells is compared with benign diploid cells in the form of DNA index. To allow for instrument error of 5%, the diploid tumours' have DNA index of 0.95 to 1.05, tetraploid tumours' 1.90 to 2.1). Flow DNA cytometric analysis provides an objective measure of DNA/chromosome abnormality and rate of cellular proliferation in a more consistent manner than subjective evaluation of histologic features.

In the study of stage I-III breast cancers by Kallioniema et al., the 6-year survival rates for patients with diploid tumour is 80%, tetraploid tumours' 60%, hyperdiploid aneuploid tumors (DNA index 1.05-1.8) about 55%, and hypertetraploid aneuploid tumours' 40%. When DNA index and S-phase fraction are combined, the best survival is found among patients with diploid
tumours' and S-phase fraction of less than 7%. The lowest survivals are those with aneuploid tumours' with S-phase fraction of greater than 12%. The remaining tumours' have intermediate prognosis.\(^{(2, 3, 4)}\)

1.7. Clinicopathlogic characteristic of invasive lobular carcinoma of the breast:
Knowledge about the biological, clinical and pathological characteristics of invasive lobular carcinoma of the breast has remained complex and unclear due to rarity of such cases.

In 1941, Stewart et al. proposed that entity of lobular carcinoma as a type of breast cancer. They described both an invasive form and in situ form of the disease which was confined to lobule and terminal ducts.\(^{(2)}\)

Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer after invasive ductal carcinoma, and accounts for 5-15% of all breast cancer in Europe and United States, respectively. The incidence of invasive lobular carcinoma in Japan was approximately 1-4% among all breast cancers.\(^{(7)}\)

A recent epidemiologic study indicated that the incidence of this type of breast cancer is increasing especially among the postmenopausal women.\(^{(6, 7)}\) Reports indicated that the use of combined oestrogen and progesterone hormone
replacement therapy increased the risk of all types of breast cancer, especially invasive lobular carcinoma.\(^7\)

Incidences rates of lobular cancer are rising faster than the rates of ductal carcinoma (USA), and postmenopausal hormone therapy may be more strongly related to lobular cancer risk than ductal cancer risk.\(^9\)

The variation in reported incidence is most probably due to different histopathological criteria used to define invasive lobular carcinoma rather than a real variation incidence. The definition of lobular carcinoma is based on cytomorphologic characteristics and absence of ductal formation.\(^{4,17}\)

Because invasive lobular carcinomas (ILC) lesions are less common and other several subtypes including alveolar, solid, tubulo-lobular, signet ring cell and pleomorphic subtypes, it is somewhat difficult to describe the clinical characteristics categorically. However, some of the clinical features have been reported to be (1) multicentric development in the same or the adjacent breast proportions than other types of breast cancer, (2) ill-defined margins and subtle thickening or indurations observed in mammography (finding of architectural distortion), (3) more frequent expression of oestrogen receptors(ER) and (4) gastrointestinal and peritoneal metastasis. Although there are several differences in the clinicopathological characteristics of ILC and invasive ductal
carcinoma, both types of carcinoma are usually managed using the same strategy.\(^{(4, 6, 7)}\)

A series comprises 301 consecutive classic lobular breast carcinomas seen at one institution between 1994 and 2001, compared to an equal number of invasive ductal carcinomas at the same institution during the same period, matched for year of surgery, age, menopausal status, primary tumor size, nodal involvement, hormone receptor status and where possible histological grade. Despite matching, the lobular carcinomas were more frequently multifocal, had more involved nodes, lower grade and lower proliferative fraction. There was no significant difference in disease-free or overall survival, locoregional relapse or time to distant metastasis between the lobular and the lobular group showed a trend to earlier appearance of contralateral breast cancer.\(^{(10,12)}\)

1.8. Gross pathology for lobular carcinoma:

Invasive lobular carcinomas present mostly as an irregular, infiltrating, poorly delineated mass rather than a sharply demarcated lesion. Invasive lobular carcinomas often display multifocality in the ipsilateral breast and have a higher tendency to develop bilaterality than other tumor types. The size of the invasive component varies considerably (from millimeters to several centimeters).
The edges of the tumor mass are often difficult to evaluate and may be best appreciated by palpation. The cut surface often appears as an inconspicuous, grey or white area. In other cases there is no grossly visible mass and the tumour can only be appreciated by palpation or not at all.

Some invasive lobular carcinomas have a macroscopic appearance identical to that of infiltrating ductal cancers. However, in many cases no mass lesion is grossly evident, and the excised breast tissue may have a normal or only slightly greater firm consistency. Thus, the microscopic size of invasive lobular carcinoma may be significantly greater than that measured grossly.(3,4,6)

1.9. General histological features for invasive lobular carcinoma:

The original definition of invasive lobular carcinoma comes from Stewart and Foote, who described the classical infiltrative subtype.

Invasive lobular carcinomas display characteristic cytologic features and a distinct infiltration pattern of the stroma. Classical invasive lobular carcinomas are composed of single cells, infiltrating in strands. In some cases focal tubule formation is seen.(4)

The classic pattern of invasive lobular carcinomas are characterized by a small uniform cell population, lacking cohesion and invading the stroma as individual tumor cells, resulting in a ‘single-file’ or Indian-file’ pattern of growth. Sometimes tumor cells are located around benign ducts in a circular
fashion resulting in a targetoid appearance. Tumor cells usually have a round or oval nucleus, thin eccentrically cytoplasm, often containing intracytoplasmic lumina (Martinez, 1979). The nucleoli are usually absent or inconspicuous. Mitotic figures are rare.

The classical form of invasive lobular carcinoma is often accompanied by in situ lesions of lobular neoplasia occurring in 40–60% of invasive carcinomas. Invasive lobular carcinoma is sometimes accompanied by a prominent lymphocytic or granulomatous reaction. The histological diagnosis of classical lobular carcinomas requires at least 70% of single file growth pattern.\(^{(2,3,4,8,11)}\)

1.10. Special subtypes of invasive lobular carcinoma:

Several histological variants of invasive lobular carcinoma have been described previously (Fechner; 1975; Fisher et al., 1979; Martinez, 1979; Dixon et al., 1982). Each subtype is named according to its growth pattern:\(^{(11)}\)

- **Classical variant:** Infiltrates in a diffuse manner through tissues without architectural distortion and which has tumour cells that are arranged in narrow cords, so called ‘Indian files’, and that surround normal structures in targetoid fashion (Fechner, 1975; Martinez, 1979).

- **Solid pattern:** This pattern is characterized by sheets of uniform cells, lacking cohesion, resulting in a growth pattern in large confluent areas with little or absent stroma in between.
• **Alveolar pattern**: In this variation tumor cells are arranged in small clusters or nests of approximately 20 cells, separated by delicate fibrovascular septa.

• **Trabecular pattern**: This variant represents a histological overlap between classical and so called trabecular filing pattern. This morphological coincidence is due to the morphological similarity between ‘single file’ seen in the classical variant and ‘one-cell thick trabecules’ observed in the trabecular variant.

• **Tubulolobular pattern**: This lesion is composed of small tubular structures as well as of single cell files seen in classical lobular carcinomas. This category represents a morphological overlap between invasive tubular and invasive classical lobular carcinoma, traditionally categorized as a variant of invasive lobular carcinoma.

• **Pleomorphic variant**: This variant represents a distinct subtype of invasive lobular carcinoma with similar growth pattern and stroma infiltration as seen in other subtypes. However, the tumor cells are larger and exhibit more cellular atypia and pleomorphism. The cytoplasm is more abundant and it often shows some eosinophilia. Recurrence free survival is reportedly poorer in pleomorphic lobular carcinomas than in classical lobular carcinomas. Pleomorphic lobular carcinomas can display apocrine, signet ring cell and
histicytoid differentiation. Apocrine differentiation in invasive lobular carcinomas has been found to have an especially aggressive clinical course.

- **Histiocytoid variant**: In this variant tumor cells have a pale appearance with foamy cytoplasm and mild nuclear variation.

- **Signet cell variant**: This subtype occurs in invasive breast carcinomas with a growth pattern of a lobular carcinoma, consisting of a prominent component of signet ring cells.

- **Mixed lobular carcinomas**: This group shows an admixture of classical lobular carcinoma accompanied by at least one more additional pattern, which could be either a special type of invasive lobular carcinoma or of invasive ductal carcinoma.\(^{(4,8,11,13)}\)

### 1.11. Grading of invasive lobular carcinoma:

Grading of invasive lobular carcinomas is widely accepted in routine surgical pathology despite the fact, that the application of BRE Score is somewhat special in this tumor type. There is no tubular formation in invasive lobular carcinomas; therefore, a score of 3 has to be attributed for tubule formation. Mitotic activity is usually low (score 1 or 2), nuclear pleomorphism can vary from monotonous to largely pleomorphic nuclei vary from monotonous to largely pleomorphic nuclei (score 1 to 3). Therefore, the majority of invasive lobular carcinomas are classified as grade 2, due to moderate nuclear
pleomorphism and low mitotic rate. Classical lobular carcinomas can be graded as grade 1, if tumor cells exhibit round small monotonous nuclei. Pleomorphic lobular carcinomas can be also graded as grade 3 if sufficient mitotic figures are present.\(^{3,4,8,13,17}\)

1.12. Differential diagnosis for invasive lobular carcinoma:

**Lymphatic proliferation:**

Invasive lobular carcinomas can closely resemble an atypical lymphatic proliferation. This diagnostic challenge preferentially occurs with suboptimal tissue fixation.

The use of immunohistochemistry (cytokeratin the neoplastic cells) or the detection of cytoplasmic in vacuoles containing mucin, should easily identify the lesion as invasive lobular carcinoma. Rarely, inflammatory cells can mimic invasive lobular cancer cells, which can be challenging particularly on frozen sections. The evidence of in situ components, lobular neoplasia, may be helpful in such settings.\(^{4,16}\)

**Invasive ductal carcinoma:**

The distinction between lobular and ductal carcinomas can pose a diagnostic difficulty based on histology alone. Invasive ductal carcinomas can display a growth pattern similar to invasive lobular carcinomas since tumor cells spreading in single files can occur in invasive ductal carcinomas. The evidence
of peri- or intratumoral lobular neoplasia (LN) or ductal carcinoma in situ (DCIS) may be of some help, however this is of limited value as in-situ components can be present independently of the histology of the invasive component. Intracytoplasmic vacuoles and areas of single cell infiltration favor the diagnosis of invasive lobular carcinoma. Immunostains for E-Cadherin, hormone receptors, gross-cystic disease fluid protein, p120 can carcinoma. Immunostains for E-Cadherin, hormone receptors, gross-cystic disease fluid protein, p120 can support the correct diagnosis.

Generally, the absence of E-Cadherin expression on the cell membrane and in most cases strong hormone receptor expression favor the diagnosis of invasive lobular carcinoma.

In addition to their different histologic appearance and mammographic characteristics, there are distinct prognostic and biologic differences between infiltrating lobular and ductal cancers.

1. Infiltrating lobular carcinomas have a higher frequency of bilaterality and multicentricity than infiltrating ductal carcinoma.

2. Infiltrating lobular carcinomas arise in older women and are larger and better differentiated tumors. As a rule invasive lobular carcinomas are ER-positive, with variant lesions showing occasional variable expression.
3. While older series report as similar prognosis for infiltrating lobular cancer and invasive ductal lesion, more recent reports suggest that outcomes (at least in the short-term) may be more favorable for lobular cancers and improving over time. However, variants of infiltrating lobular carcinomas exist, some of which have poor prognosis.

4. As a group, invasive lobular carcinomas tend to metastasize later than invasive duct carcinomas and spread to unusual locations such as peritoneum, meninges, and the gastrointestinal tract.

Lobular breast cancers have been observed to occur in 20% to 54% of women from families who carry mutations in the E-cadherin (CDH1) gene, which is associated with hereditary diffuse type gastric cancer. Approximately 50% of sporadic lobular breast cancers have E-caderin mutations.\(^{(3,4,6,7)}\)

**Fat necrosis:**

The histiocytoid variant of invasive lobular carcinoma may be particularly difficult to differentiate from fat necrosis in some instances, as tumor cells can mimic reactive histiocytic infiltration and vica versa. Immunohistochemistry for macrophage markers (e.g. CD 68) and cytokeratins should lead to the correct diagnosis.\(^{(4)}\)
1.13. immunohistochemistry:

Hormone receptors:

The large majority of invasive lobular carcinomas show strong expression of estrogen and progesterone receptors, a higher rate than in invasive ductal carcinomas.\(^{(3,7,11)}\)

Her2 gene and protein:

Her2 protein expression and/or gene amplification are rare events in invasive lobular carcinomas. The pleomorphic variant of invasive lobular carcinomas represents an exception to this rule, as Her2 gene amplification and protein expression, particularly in grade 3 cases have been described in the literature.\(^{(3,6)}\)

Proliferation index (MIB-1):

Proliferation index is generally low in invasive lobular carcinomas. In some studies distinct differences in proliferation activity were detected in classical versus pleomorphic subtypes varying from 2.9% (classical type) to 8–11% (pleomorphic variants). The proliferation fraction of invasive ductal carcinomas is usually higher; in grade 3 cases the MIB-1 labeling index often reaches 25–30% or even higher.\(^{(4)}\)
**E-Cadherin:**

The transmembrane protein E-Cadherin which mediates cell-cell adhesion and acts as an invasion suppressor factor had been reported to be a reliable marker in the differentiation of ductal and lobular breast carcinomas. Ductal carcinomas usually express membranous E-Cadherin reactivity, while invasive lobular carcinomas are mostly negative. Therefore, the absence of E-Cadherin positivity is a significant finding in the diagnosis of invasive lobular carcinomas. Together with conventional histology, a negative E-Cadherin reaction is the most helpful immunohistochemical marker conversely, in a subset of poorly differentiated invasive ductal carcinomas (less than 15%), E-Cadherin may be absent. In these cases other morphological features such as tubule formation, hormone receptor status and additional immunohistochemistry are needed to confirm the diagnosis of an E-Cadherin negative invasive ductal carcinoma.\(^{(3, 4, 6, 8, 11)}\)

**P120:**

The interaction of E-Cadherin with catenins such as p120 has been documented in previous studies. Cytoplasmic positivity for p120 generally favors the diagnosis of lobular carcinoma, as membranous reaction has mostly been reported in invasive ductal carcinoma.\(^{(3, 4)}\)
**GCDPF-15 (gross cystic disease fluid protein):**

Approximately one third of the invasive lobular carcinomas are positive for GCDPF-15, a marker for apocrine differentiation. Invasive lobular carcinomas with histiocytoid, pleomorphic or signet ring cell components tend to express GCDPF-15. Positivity for this marker however does not necessarily confirms the diagnosis of invasive lobular carcinoma, as GCDFP-15 can be seen in other breast cancer subtypes such as apocrine, endocrine, oncocytic and acinic cell carcinomas and some positivity has been reported in invasive ductal carcinomas as well.\(^{(4)}\)

**Cytokeratin:**

Invasive lobular carcinomas are reportedly negative for cytokeratin.\(^{(5,6)}\) In recent studies a subset (15%) of invasive lobular carcinomas tested positive for cytokeratin/6, which also were preferentially hormone receptor negative, leading to postulating a distinct basal like ILC subtype. However, no definite morphological differences could be found upon cytokeratin 5/6 positivity among invasive lobular carcinomas.\(^{(3,10,12,13)}\)

**Cyclin D1:**

Cyclin D1 can evoke hormone receptor activation through binding to estrogen receptors. Overexpression of Cyclin D1 has been reported in over 80% of
invasive lobular carcinomas. However, this positivity is not specific for a definitive lobular differentiation, as it can occur in other subtypes as well.\(^{(4,10)}\)

**1.14. Prognoses for invasive lobular carcinoma:**

In general, prognosis of invasive lobular carcinomas does not consistently differ from invasive ductal carcinomas. However when histological subtypes of ILC are analyzed one by one, a more favorable outcome has been reported for the classical type of invasive lobular carcinoma. In some studies, the pleomorphic and the signet ring cell variants have been associated with poorer outcome. Also, the metastatic pattern of invasive lobular carcinomas differs from invasive ductal breast carcinomas. Higher rates of bone, gastro-intestinal tract, meningeal and/or ovarian metastases have been documented in invasive lobular carcinomas.\(^{(4,6,7,15,16)}\)

In a study of 230 patients with stage 1 and 11 invasive lobular carcinoma treated by mastectomy and axillary lymph node dissection, 176 showed the classical or Indian file pattern of (ILC) and 54 patients showed variant histology (solid), alveolar, and mixed patterns). ILC (Classic) patients were younger than variant patients, and more likely to be premenopausal.\(^{(10)}\)

Invasive lobular carcinoma (ILC) of classical or Indian –file microscopic architectural pattern is approximately 85%-90% and of more favourable prognosis than variant subtypes of ILC.\(^{(11)}\)
In one study of 138 patients had presented with invasive lobular carcinoma (ILC) over a period of 20 years. Histological subtypes of ILC and vascular invasion played a role in the biologic behaviour of the tumour. Interestingly premenopausal status protected against the risk of relapse, while being postmenopausal, increased the risk.\textsuperscript{(12)}

One hundred and seventy-one cases of operable invasive lobular carcinoma, presenting over an 11-year period, were reviewed. Histological subtypes were investigated to determine differences in their clinical behaviour and whether these differences could be explained by histopathological features.

Five subtypes were identified: mixed (45.6%), classical (30.4%), tubulo-lobular (13.5%), solid (6.4%) and alveolar (4.1%). The tubulo-lobular tumours were more likely to be of good histological grade and node negative.

The other three subtypes did not differ significantly in their histopathological parameters, reflected in similar clinical behaviour. They occupied an intermediate position between the other two subtypes in terms of prognosis.\textsuperscript{(4,10,11,12)}
OBJECTIVES

General objectives:
To highlight the clinico-pathological characteristics of invasive lobular carcinoma of the breast; and to identify the incidence rate at National Health Laboratory (NHL), from 2005 to 2009.

Specific objectives:
• To study morphological features of invasive lobular carcinoma of the breast (ILC).
• To outline the clinical characteristics of invasive lobular carcinoma (ILC).
• To compare the incidence rate of invasive lobular carcinoma with other invasive carcinomas of the breast.
• To identify the estrogen and progesterone receptors (ER/PR) status of ILC.
2. MATERIALS AND METHODS

Study design:
This is a descriptive, archival and retrospective study.

Study area:
The study conducted at National Health laboratory in Khartoum (NHL); over period of five years (2005-2009).
All file recorded cases of invasive carcinoma of the breast were collected and reviewed to identify the incidences rates; and with special consideration on clinophalological features of invasive lobular carcinoma.

Materials:
The clinical and histological data of patient’s records, from the National Health Laboratory in the Sudan were collected and reviewed.
A total of 508 patients from archives pathology reported files as Invasive breast carcinoma from period over five years (2005-2009) were collected. The data collected includes age, type of specimen (i.e. Mastectomy or/and biopsy specimens), histological type and grade, lymph node involvement and hormonal status (ER & PR).
Haematoxylin and eosin stained glass slides from formalin fixed, paraffin embedded tumour tissue in 33 of 508 patient diagnosed as invasive lobular carcinomas of the breast.

**Criteria of selection:**

All archive pathology reported as invasive lobular carcinoma in National Health Laboratory records during years 2005-2009 were included in the study. The data collection sheet designed to include patient’s clinical information, specimen type, histological type, histological malignancy grade, lymphatic invasion and hormonal receptors status.

Other invasive breast carcinoma (invasive ductal, special histological and clinical subtypes) and male invasive lobular carcinoma are excluded in this descriptive, retrospective study.

**Methods:**

The clinical and pathological characteristics of 33 patients with invasive lobular carcinoma who underwent surgery were reviewed. All the sections obtained from formalin fixed, paraffin-embedded blocks of surgical specimens were stained by H & E for histological evolution and immunohistochemical staining for Estrogens and progesterone receptor (ER &PR) were re-examined by light microscopy.
The evaluation of the 33 invasive lobular carcinoma (ILC) include recording of the following features: Diagnosis or histological type and classified subtypes, histological malignancy grade, vascular and lymphatic invasion and hormone receptors for tumour characterization. Regarding the diagnosis, two categories were used: Classical ILC subtypes and other non-classical subtypes (Solid, tubulo-lobular, pleomorphic, and singnet ring cells, alveolar and mixed subtype). Histological malignancy grading was performed according to the modified Bloom and Richardson grading system where the combination of three histological features was evaluated: Percentage of tubules formation, nuclear pleomorphism and mitotic count. Multifocality was defined by at least two tumour foci apart.

During the histological assessment of 33 cases of invasive lobular carcinoma, 3 cases were ruled out (excluded) and categorized histologically as invasive ductal carcinoma special subtypes. ER and progestrone receptor (PR) in the malignant tissue were measured by an enzyme immunoassay, or immunohistochemical staining of sections taken from formalin-fixed, paraffin-embedded blocks of surgical specimens. 20 sections were assessed for hormonal receptors and others 10 from patient’s files records. The determinations of levels of hormone receptors were considered positive at least 10% or greater of the nuclei of the tumour cells in the invasive part of the
tumour, show a detectable positive reaction in oestrogen and/or progesterone receptor staining.

**Statistical analysis:**

The data were analyzed using a computer statistical software called SPSS (originally, statistical package for the Social Sciences) to determine the frequency and percentage.
3. RESULTS

From a total of 508 archived file reported pathology of invasive breast carcinomas between 2005-2009 at national health laboratory. We identified 411 (80.9%) patients with invasive ductal carcinoma (IDC), 30 (5.9%) patients invasive lobular carcinoma (ILC) and 67 (13.2%) patients with others histological and clinical types of breast carcinomas (Table 1).

On the studied materials 30 (5.9%) of invasive lobular breast carcinoma 27 (90%) were classical types and 3 (10%) recognized as signet ring and pleomorphic subtypes. The other variants of invasive lobular breast carcinoma (solid, alveolar, tubulo-lobular, pleomorphic and mixed) were not identified in the evaluated material in this study.

The incidence rates of both invasive ductal and lobular carcinoma match with most of the reported studies regardless of variability of provided materials for analysis. It is realized in this descriptive study, there is a significant increased incidence of mastastatic carcinomas, 13 (2.5%) of all invasive breast carcinomas, to the breast without identifying the primary or original sites (Table 2).

The average age of the patients was 57.5 years (range, 30-85 years) and 5.3 (range, 25-82 years old) in patients with invasive lobular carcinoma, and other types of invasive breast cancers (Invasive ductal and other special types),
respectively. The majority of patients falls in range of age (40-49 years), 163(32.1%) for all invasive breast carcinomas, and 12(40%) of invasive lobular carcinoma. Significantly, in the subject include 30 patients of invasive lobular carcinoma, 18(60%) were in postmenopausal age, while 12(40%) at premenopausal age (Table 3).

Regarding the histological malignancy grade in all invasive breast carcinomas, grade 1 were 58(11.4%), grade 2 comprises 196(38.6%), grade 3, 135(26.6%) and 111(21.9%) not determined or classified (Figure 3).

The histological malignancy grade in invasive lobular carcinoma of the 30 histologically evaluated materials are categorized as grade 1, 5(16.7%), grade 2, 22(73.3%), and grade3, 3(10%). Most of the tumours are grade 2(table 3). This is not suppressing considering the grading method and tumour morphology. The invasive lobular carcinoma is mostly of classical subtypes which consist of rather small tumour cells, growing in single filling without tubule formation. The number of mitosis is limited, which leaves the nuclear pleomorphism as determining factor.

In relation to age distribution with tumour histological grade in invasive lobular carcinoma, considerable number patients lies in age range of 40-49 years, 12(40%) and postmenopausal age (Table 3).
Invasion of lymphatic especially axillary group of lymph node is a significant pathological characteristic of most of invasive breast carcinomas. Regarding lymph node status, in the studied materials 160(31.5%) patients with lymph node involved and 324(63.8%) revealed no involvements (Figure 5).

In the evaluated (30) patients of invasive lobular carcinomas 12(40%) lymph node involved compared to 18(60%) with no involvements (Table 4).

If lymph node status is compared to histological malignancy grade, there is a significant correlation, showing increased number of positive lymph nodes among the grade 2 tumours.

8(67%) out of 12 lymph node involved with invasive lobular carcinoma, are grade 2, and 4(33%) grade 3.

Relating lymph node status in invasive lobular carcinoma to age distributions, relative numbers of tumours are in age range of 40-49 years, 5(42%) lymph node involved and 7(58%) no involvement. Similarly, 5(42%) and 7(58%) of lymph node involved are in the postmenopausal and premenopausal age respectively.

The percentage of lymph node metastasis tends to be lower in invasive lobular carcinoma as well as in the all invasive breast cancer.

From 508 patients 225(44.3%) of invasive breast carcinomas were asses for hormone receptors, while 277(54.5%) not assesses (Figure 5). Similarly,
30(100%) of invasive lobular carcinoma of the breast were evaluated for hormone receptors. Invasive lobular breast carcinoma predominantly is a hormone receptor positive, regardless of type. However, there is significant correlation between hormone receptor status and grade, with increased incidence of receptor positive tumours 15(50%) with grade 2 and negative tumours among grade 3.

The proportion of ER and PR positive tumours was 21(70%), and 15(50%) and negative 9(30%) and 15(50%) in the invasive lobular carcinoma (Table 5).

The tumours reactivity for hormones receptors (ER and PR) are categorized as ER/PR positive, 12(40%), ER+/PR-, 9(30%), ER-/PR+, 3(10%), and ER/PR negative 6(20%) in the studied materials for invasive lobular carcinoma (table 6). The determination of levels of hormone receptors is considered positive when at least 10% or greater of the nuclei of the tumour cells in the invasive part of tumours.
Table 1: Incidence rates of histological types of Invasive breast carcinomas

(n = 508)

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC</td>
<td>411</td>
<td>80.9</td>
</tr>
<tr>
<td>ILC</td>
<td>30</td>
<td>5.9</td>
</tr>
<tr>
<td>Others</td>
<td>67</td>
<td>13.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>508</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 2: Distribution of special histological and clinical types of breast carcinoma malignancies (n = 67)

<table>
<thead>
<tr>
<th>Special subtypes</th>
<th>Frequency</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraducal carcinoma (In-Situ)</td>
<td>12</td>
<td>2.4%</td>
</tr>
<tr>
<td>Invasive papillary carcinoma</td>
<td>8</td>
<td>1.6%</td>
</tr>
<tr>
<td>Invasive mucinous carcinoma</td>
<td>7</td>
<td>1.4%</td>
</tr>
<tr>
<td>Medullary breast carcinoma</td>
<td>5</td>
<td>0.9%</td>
</tr>
<tr>
<td>Metaplastic carcinoma</td>
<td>4</td>
<td>0.8%</td>
</tr>
<tr>
<td>Metastastic carcinoma</td>
<td>13</td>
<td>2.5%</td>
</tr>
<tr>
<td>Malignant phyllodes tumours</td>
<td>4</td>
<td>0.8%</td>
</tr>
<tr>
<td>Anaplastic carcinoma</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Malignant mesenchymal tumours</td>
<td>2</td>
<td>0.4%</td>
</tr>
<tr>
<td>Inflammatory carcinoma</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>Secretory carcinoma</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tubular breast carcinoma</td>
<td>2</td>
<td>0.4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>67</strong></td>
<td><strong>13.2%</strong></td>
</tr>
</tbody>
</table>
Table 3: Correlation of age with the histological grade of invasive lobular carcinoma in study sample (n = 30)

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Histological Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>20 -29</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>30 - 39</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>40 - 49</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>50 - 59</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>60 - 69</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>70 - 79</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>80 - 89</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5</strong></td>
<td><strong>24</strong></td>
</tr>
<tr>
<td>Lymph node status</td>
<td>Frequency</td>
<td>Percentage</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Involved</td>
<td>12</td>
<td>40.0</td>
</tr>
<tr>
<td>Not Involved</td>
<td>18</td>
<td>60.0</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100.0</td>
</tr>
</tbody>
</table>
**Table 5: Shows the proportion percentage of ER and PR status in studied population 30 patients with ILC**

<table>
<thead>
<tr>
<th>ER/PR Status</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ ER</td>
<td>21</td>
<td>70%</td>
</tr>
<tr>
<td>- ER</td>
<td>9</td>
<td>30%</td>
</tr>
<tr>
<td>+ PR</td>
<td>15</td>
<td>50%</td>
</tr>
<tr>
<td>- PR</td>
<td>15</td>
<td>50%</td>
</tr>
</tbody>
</table>
Table 6: Summarized the combined ER and PR frequency and responses in ILC

<table>
<thead>
<tr>
<th>ER/PR Status</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ ER/+PR</td>
<td>12</td>
<td>40%</td>
</tr>
<tr>
<td>+ ER/-PR</td>
<td>9</td>
<td>30%</td>
</tr>
<tr>
<td>-ER/+ PR</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>-ER/-PR</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
Figure 1: Distribution of malignant breast conditions (n = 508)
Figure 2: Age distribution in all invasive breast carcinomas (n = 508)
Figure 3: Distribution of histological grade of all invasive breast carcinoma (n = 508)
Figure 4: Distribution of the histological grade of invasive lobular carcinoma (n = 30)
Figure 5: ER/PR status of all invasive breast carcinomas among the study population (n = 508)
Figure 6: Lymph nodes status of invasive breast carcinoma among the study population (n = 508)
Carcinoma of the breast is the commonest malignancy in Sudanese females, accounting for (34.5%) of all cancers (A/Salam 2003). The incidence of female breast cancer in Sudan is among the highest in countries south of the Sahara.\(^{(16)}\) Invasive lobular carcinoma develops from the acinar epithelium of the mammary gland and frequently invades the normal tissue without provoking the abundant desmoplastic response that unusually accompanies invasive ductal carcinoma.\(^{(6)}\) Invasive lobular carcinoma is a form of invasive breast cancer that has distinctive pathologic characteristics. The classical tumour is diffusely infiltrative and is composed of small, round, regular cells that form single lines throughout a desmoplastic stroma.\(^{(16,17)}\) Invasive lobular carcinoma is the second most common type of breast cancer as indicated by many reports.\(^{(3,6,7,8,11,13,17)}\) In the current study the incidence rate is 5.9% of all invasive breast carcinomas, is in accordance with the incidence rate range of 5-10% reported in the literature for USA and Europe, but less than Japan incidence rate 1-4%.\(^{(7)}\) Reviewing the literature, no study was conducted in Africa and Sudan reflecting the biological, clinical and pathologic features of invasive lobular carcinoma as distinct type of breast cancer.
This study shows that the incidence is significantly rising, due to an overall increase in the incidence of breast cancer, and also due to increased knowledge of the different histological subtypes, resulting in accurate diagnosis.\cite{6,7}

Several studies showed that patients with invasive lobular carcinoma are on average older at presentation than are invasive ductal carcinoma.\cite{6,7,10}

Consistent with these data, in the present study the median ages at diagnosis were 57.5 years (range, 30-85 years) for patients with ILC and 5.3 (rang, 25-82 years) for patients with IDC. This older age at the time of diagnosis in those with ILC could be due to low proliferative rate or greater difficulties in detecting invasive lobular carcinoma. Significantly, in this study invasive lobular carcinoma was more common or increasing among postmenopausal women.\cite{6,9}

At the present analyzed data, the tumour histological grade for all invasive breast carcinoma is grade 2(38.6%), followed by grade 3(26.6%). Most of the invasive lobular carcinoma are grade 2(73.3%), minor portion grade 1 and only very few grade 3 tumours. This is to be expected, considering the grading method (tubule formation, number of mitoses and nuclear pleomorphism) and it correlates well with the findings in other studies.\cite{4,6,17} Invasive lobular carcinoma is mostly of the classical subtype which is morphologically consisting of rather small tumour cells, growing in single file without tubule
formation. The determining factor for histological malignancy grade in ILC is nuclear pleomorphism, as the number of mitosis is limited. Several studies showed a correlation between prognosis and histological malignancy grade in invasive lobular carcinoma.\(^{(8,16,17)}\)

A Study by (M.-L. Maller Talman et al) included 860 lobular carcinomas found a significantly worse prognosis for grade 3 tumours compared to grade 2 tumours (16). Most of grade 3 tumours are among the other variants of ILC such as solid and pleomorphic subtypes whole grade 1 and 2 tumours more commonly in the classical subtype.\(^{(8,10,11,16)}\) In this study the proportion of ILC grade 3 was only 10%, and therefore there is no significant differences in prognosis between grade 1 and 2 tumours.

Histological malignancy grading of ILC is not very common, probably due to a weakness of grading method in this type of carcinoma, where the nuclear pleomorphism often is the determining factor. However Nottingham studies finding quoted by Moller Talman et al.,\(^{(16)}\) show that the grading method is a powerful prognostic indicator.

Relating the age distribution with tumour histological grade in ILC, it was found that a patient in age range is 40-49 years and few more than 70 years. In the current study it was found that tumour histological grade 2 is more
common in postmenopausal age (65%), but this not significantly related to prognosis of ILC.

The incidence of lymph node metastasis with invasive lobular carcinoma tended to lower to (40%) in this study. This is may be due the uniform appearance of bland tumour cells that lack cellular atypia and often have a low mitotic rate making the lobular carcinoma cells more difficult to detect in metastatic lymph node. Reports indicated that the proportion of lymph node metastasis of ILC occur at the same rate in comparison to other types of invasive cancer.\(^{6,7,15}\)

In this study the percentage of lymph node metastasis tended to be slightly lower in invasive lobular carcinoma as well as in the all invasive breast cancers.

Invasive lobular carcinoma predominantly is hormone receptors positive regardless of subtypes.\(^{16}\) Few small and scattered studies have addressed the biologic features of ILC, indicating that lobular carcinomas are significantly more likely to steroid positive than other invasive cancer of the breast.\(^{6,7,16}\) This study found that 70% of tumours are ER positive and only 50% PR positive. When categorizing the tumour reactivity for hormone receptors, 40% are ER/PR positive and only 20% revealed ER/PR negative. Based on the current study finding, we can conclude that ER expression is more frequently
invasive lobular carcinoma than in other types of breast cancer. Thus, invasive lobular carcinoma is mostly hormone receptor positive.

In general, the management of the patients in data analyzed is the same for all invasive carcinoma, 60% treated by mastectomy. However, this analysis suggested that ILC was treated by mastectomy (46.7%) slightly less frequently than other invasive carcinomas. In practice, the histologic type appears to play a role in the choice of surgical procedure.\(^{(6)}\)

Although this tendency to favor mastectomy may be related to factors specific to patients and/or surgeon, the choice of these procedures is also influenced by pathologic findings. Indeed, the diminished fibrotic reaction present in ILC makes it difficult for pathologist and surgeons to determine the gross extent of the disease during surgery, and to achieve tumour-free margins after a limited excision.\(^{(6,7,16)}\)

With respect to the systemic therapy, because lobular carcinomas are more frequently steroid receptor positive tumours, as expected a greater proportion of ILC patients received adjuvant endocrine therapy.\(^{(6,7,16)}\)
CONCLUSION

- The most common specific type of invasive breast carcinoma next to invasive ductal carcinoma is invasive lobular carcinoma.
- The incidence rate of invasive lobular carcinoma is increasing as well as other types of invasive breast carcinomas.
- Invasive lobular carcinomas are more likely to occur in older patients or postmenopausal age.
- Most of the invasive lobular carcinomas are grade 2 tumours.
- The percentage of lymph node metastasis tends to be lower in invasive lobular carcinomas as well as in other invasive breast cancer.
- Invasive lobular carcinomas are more frequently hormone receptors positive, with increased incidence of receptor reaction to histological grade 2 tumours.
RECOMMENDATIONS

- Further in-depth studies are highly recommended to address the biological, clinical and pathological characteristics of invasive lobular carcinoma and other special subtype of breast cancers, to include the following:

  1- Clinical and epidemiological factors for ILC.
  2- Histological variants of Invasive lobular Carcinoma.
  3- Ductal and lobular insitu carcinoma.
  4- Prognostic factors of invasive lobular carcinoma.
  5- Full microscopic review for breast cancers.

- This study was challenged by the rarity of invasive lobular breast carcinoma, and other limitations, such as missing of some clinical information in reported files, no previous studies or reports regarding ILC and the data were collected in one center which might not give a full account of the disease. Therefore, we recommended prospective studies and records improvement.
REFERENCES


City Hospital, Nottingham NG5 IPB, UK, and 3Tenovus Institute for Cancer.

14. The anatomy and Physiology of the breast, CME, View article/548921-2


ANNEXES

Invasive lobular Carcinoma of the breast
(Working sheet)

Lab NO: ---------------------------------------------- Date: ---------------------------

Patient Name: -----------------------------------------Age: ---------------------------

Specimen Type: Excision { } Mastectomy { } other (specify) ---------

Clinical Information:
  1- Clinical presentation:----------------------------------
  2- Primary/recurrent-----------------------------------
  3- Past surgery:--------------------------------------
  4- Mammography finding----------------------------------

Gross findings (specific for ILC):

-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------

Microscopic findings (specific for ILC):

-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
**Histological type:**

1- Invasive Ductal Carcinoma, IDC [ ]

2- Invasive lobular carcinoma, ILC (Classic type) [ ]

3- Invasive lobular carcinoma variants [ ]

4- Other Invasive breast carcinoma [ ]

**Histological grade:**

1- **Grade 1:**
   - Tubules formation [ ]
   - Nuclear pleomorphism [ ]
   - Mitotic count/10HPF [ ]

2- **Grade 2:**
   - Tubule formation [ ]
   - Nuclear Pleomorphism [ ]
   - Mitotic count/10HPF [ ]

3- **Grade 3:**
   - Tubules formation [ ]
   - Nuclear pelomorphism [ ]
   - Mitotic Count/10HPF [ ]

4- **Grade cannot be determined**

**Lymph node involvement:**

- Involved [ ]
- not involved [ ]

**ER/PR Status:**

- Positive [ ]
- Negative [ ]
<table>
<thead>
<tr>
<th>Age</th>
<th>Specimen Type</th>
<th>Histological Types</th>
<th>Histological Grade</th>
<th>Lymph Involvement</th>
<th>Nodes</th>
<th>ER/RE Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biopsy</td>
<td>M.Tomy</td>
<td>IDC</td>
<td>ILC</td>
<td>ILC(V)</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not Involved</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Result</td>
</tr>
</tbody>
</table>
Invasive lobular carcinoma
Invasive lobular carcinoma