Invasive Carcinoma NST

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Synonyms

Carcinoma simplex; Ductal NST; Infiltrating ductal carcinoma; Invasive carcinoma of no specific type (NST); Invasive ductal carcinoma not otherwise specified (ductal NOS); Scirrhous carcinoma; Spheroidal cell carcinoma

Definition

Invasive breast carcinoma of no special type is also commonly known as invasive ductal carcinoma not otherwise specified, comprises the largest group of invasive breast cancers. It is a morphologically heterogeneous group which does not exhibit the features or purity of tumors of recognized special types of breast cancer, such as classical invasive lobular (▶ Invasive Lobular Carcinoma) or tubular carcinoma (▶ Invasive Tubular Carcinoma).

Clinical Features

- **Incidence**: Invasive carcinoma NST forms a large proportion of mammary carcinomas and its epidemiological characteristics are similar to those of breast cancer as a whole. The WHO currently identifies that breast cancer is the most frequent cancer among women, impacting 2.1 million women each year, and also causes the greatest number of cancer-related deaths among women. In 2018, it is estimated that 627,000 women die from breast cancer – that is approximately 15% of all cancer deaths among women. While breast cancer rates are higher among women in more developed regions, rates are increasing in nearly every region globally.
- **Age**: It is rare below the age of 40 years, but the proportion of tumors classified as such in young women with breast cancer is in general similar to that in older women.
- **Sex**: Breast cancer of NST is a disease predominantly of females with male breast cancer being very rare. Less than 1% of all breast cancer cases develop in men, and only one in a thousand men will ever be diagnosed with breast cancer.
- **Site**: Breast cancer of NST occurs in the parenchyma of the breast or very rarely in extra mammary ectopic breast tissue. Approximately 50% of breast cancers arise in the upper outer quadrant of the breast, 15% in the

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inner upper quadrant, and <10% in the inner lower and outer lower quadrants respectively.

- **Treatment**: The management of breast cancer of NST depends on the prognostic characteristics of the tumor including the histological grade (or growth fraction), size, lymph node stage, vascular invasion, hormone receptor, and HER2 receptor status of the cancer. Treatments are more aggressive when the prognosis is worse or there is a higher risk of recurrence of the cancer following treatment. Surgery with or without radiation therapy is the usual initial treatment in early stage disease, which may be followed by adjuvant systemic therapy such as endocrine therapy, chemotherapy, and targeted anti HER2 therapy where appropriate. Approximately, 70–80% of NST breast cancers are estrogen receptor (ER)-positive and 12–20% of cases are HER2 positive.

  Neoadjuvant chemotherapy (NACT) has been shown to be effective in downstaging breast cancer and is now commonly used as primary therapy (Early Breast Cancer Trialists' Collaborative Group 2018). NACT for early breast cancer can make breast-conserving surgery more feasible. Patients with high-grade, hormone receptor-negative tumors are most likely to achieve a complete clinical response of the primary tumor after NACT. Pathological complete response (pCR) of the axilla can be achieved in 41–75% of patients with HER2-positive or triple-negative cancer receiving NACT.
- **Outcome**: Outcomes for breast cancer vary depending on the extent of disease, prognostic characteristics and response to treatment. Survival rates have improved significantly in recent years due to multiple variables including early detection, screening and an increasing range of effective treatment options. Survival rates in the developed world are now high, with between 80% and 90% of those in Europe and the United States alive for at least 5 years. In developing countries survival rates are poorer.

  Tools and methods have been developed to assist in predicting patient outcome and to support clinical decision making in breast cancer management. Examples of such methods include the Nottingham Prognostic Index (NPI) (Blamey et al. 2007), St Gallen consensus criteria, the National Comprehensive Cancer Network (NCCN) guidelines, and Predict (https://www.predict.nhs.uk).

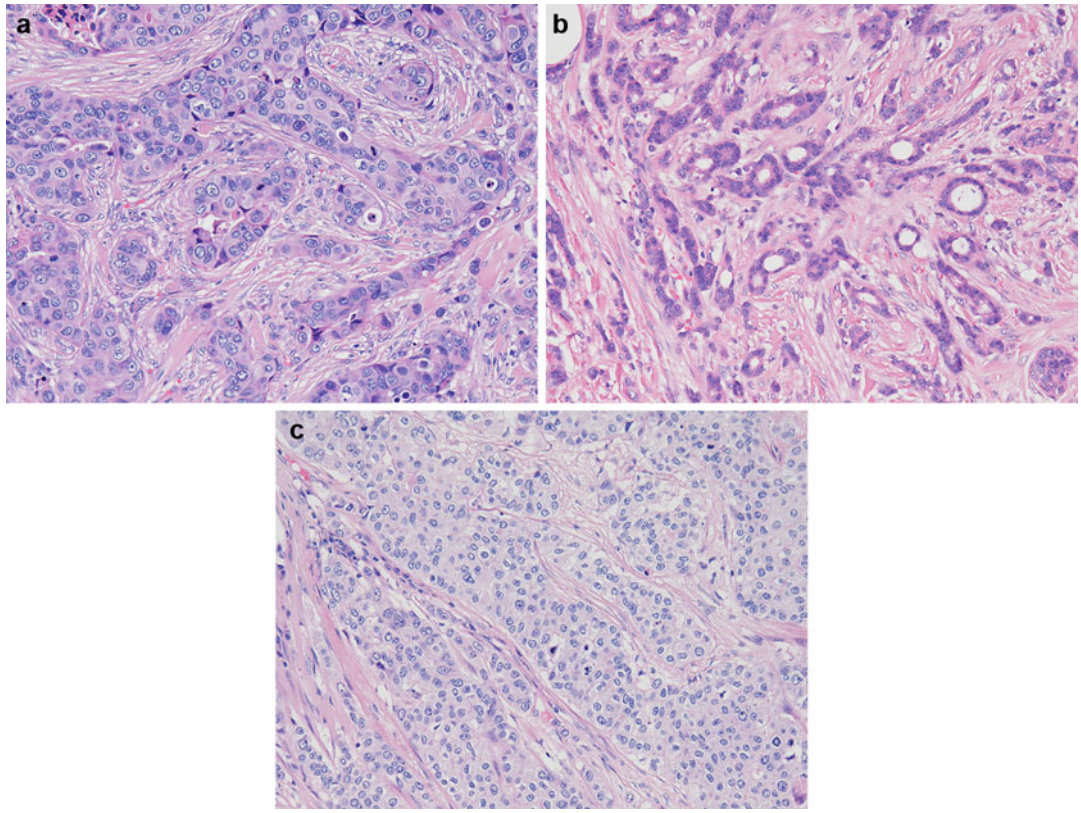
  The NPI is based on a combination of histopathological examination of tumor size, lymph node stage, and tumor grading assembled in a prognostic index formula. Prognosis worsens as the NPI numerical value increases and by using cut-off points patients may be stratified into good, moderate and poor prognostic groups. The NPI has been confirmed after long-term follow-up, validated independently in large multi-center studies, and revised in order to stratify patients into 5 prognostic groups (Blamey et al. 2010).

Macroscopy

Due to their morphological, biological, and behavioral diversity, these tumors have no specific macroscopic features. They can range in size from <10 mm to >100 mm. They can have a rounded, irregular, stellate, diffuse, or nodular configuration. The invasive border is variable in appearance but usually moderately or ill-defined and lacks sharp circumscription. Classically, NST carcinomas form a mass lesion and are firm or even hard on palpation, and may have a "gritty" feel when cut with a blade. The cut surface appearance is varied but is usually pale and grey to cream white.

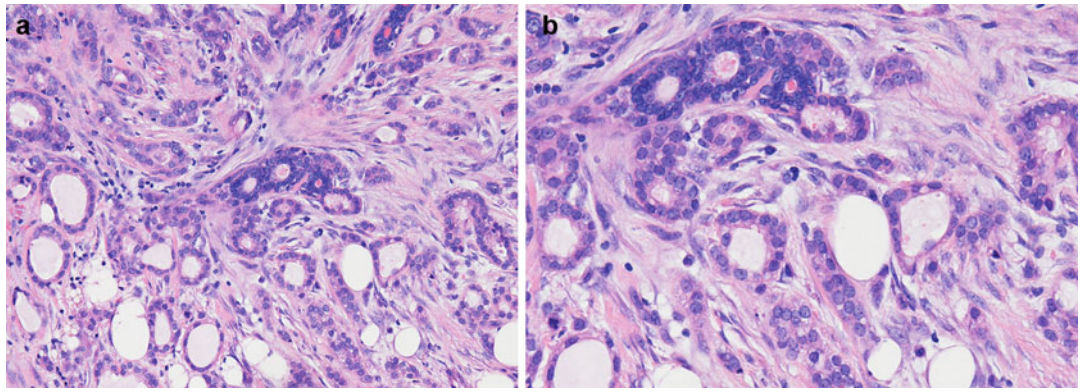
Microscopy

Assignment of a tumor to the NST histological type of breast cancer is essentially through a process of exclusion of recognized special types. As a consequence, morphological features vary considerably from case to case. All types of tumor margins can be observed, from highly infiltrative, invading nonspecialized mammary stroma, and disrupting the normal parenchymal lobular architecture to continuous pushing margins. Architecturally, the tumor cells may be arranged in cords,



Invasive Carcinoma NST, Fig. 1 (**a**, **b**, **c**) Examples of three invasive carcinomas of NST type showing no specific characteristics and a range of morphological appearances. Note the lack of special characteristic exhibited by each tumor and also the range of morphological appearances seen in the NST tumor type. Please note that all the figures in this chapter are of NST tumours, with the exception of Fig. 2 which shows a tumour of missed type with both NST and Tubular features

clusters, and trabeculae, while some tumors are characterized by a predominantly solid or syncytial infiltrative pattern with little associated stroma (Fig. 1a, b, c: all the figures in this chapter illustrate examples of NST histological type, please note the ranges of non specific appearances). In many of cases, glandular differentiation may be apparent as tubular or acinar structures with central lumina formed by the tumor cell population. Occasionally, areas with single-file infiltration or targetoid features mimicking invasive lobular carcinoma (▶ Invasive Lobular Carcinoma) occur but lacking its distinct cytomorphological characteristics. NST carcinoma cells have a variable appearance. Their cytoplasm may be abundant and eosinophilic. Nuclei may be regular and uniform or highly pleomorphic with prominent, often multiple, nucleoli. Mitotic activity ranges from virtually absent to frequent. In up to 80% of cases, foci of associated ductal carcinoma in situ (DCIS) (▶ DCIS) will be present. Any associated DCIS is usually of same nuclear grade as the invasive carcinoma. Occasionally lobular neoplasia, either ALH or LCIS may be present (▶ Lobular In Situ Neoplasia). The stromal component is extremely variable. There may be a highly cellular fibroblastic proliferation, a scanty element of connective tissue or marked hyalinization. Foci of elastosis may also be present in a periductal or perivenous distribution. Focal necrosis may be present and this is occasionally extensive with secondary formation of cysts. In a minority of cases, a distinct lymphoplasmacytoid infiltrate can be identified.



Invasive Carcinoma NST, Fig. 2 (**a**, **b**) An example of a tumor of mixed type with focal (>50% and <90%) tubular carcinoma characteristics with background (<50%) non specialised, NST, features. Please note that this tumour shows grade 1 histological characteristics. Note the presence of a normal lobular unit (**b**) for comparison of tumor cells' nuclear size. The carcinoma has similar sized nuclei and score 1 for nuclear pleomorphism. There is marked tubule/gland formation, score 1 and no visible mitoses, score 1, giving a total score of 3 (grade 1)

Vascular tumor emboli can be observed within or adjacent to the tumor.

Carcinoma of Mixed Histological Type

The current UK (Ellis et al. 2016), European (Perry et al. 2006) and WHO (Lakhani et al. 2012) classification systems promote use the mixed tumor type category for tumors which lack the purity of a specific special type but show prominent or dominant but not pure special type characteristics. For a tumor to be typed as breast carcinoma NST, it must have a non-specialized pattern in >50% of its mass as judged by thorough examination of representative sections. If the NST pattern comprises between 10% and 49% of the tumor, the rest being of a recognized special type, then it will fall into one of the mixed groups: mixed NST and special type (Fig. 2) or mixed NST and lobular carcinoma. Apart from these considerations, there are very few lesions that should be confused with NST carcinomas.

Rare Morphological Variants of NST Carcinoma

The current WHO classification of breast tumors (Lakhani et al. 2012) recognizes a number of morphological forms of breast cancer that are not currently recognized as distinct special types of invasive breast cancer but as variants of NST breast cancer. These include pleomorphic carcinoma, carcinoma with osteoclast-like stromal giant cells, carcinoma with choriocarcinomatous features, and carcinoma with melanotic features. There is also a current debate whether to include medullary like cancers within a group of NST cancers with associated lymphocyte-rich stroma rather than as a distinct separate morphological type.

Pleomorphic carcinoma. The 2012 WHO classification defines pleomorphic carcinoma as a rare variant of high-grade NST carcinoma, which is characterized by a proliferation of pleomorphic and bizarre, sometimes multinucleated, tumor giant cells comprising >50% of the tumor cells in a background of adenocarcinoma or adenocarcinoma with metaplastic spindle and squamous differentiation. The tumors are typically of grade 3 with a high mitotic frequency and central necrosis.

Carcinoma with osteoclast-like stromal giant cells. The 2012 WHO classification defines these carcinomas by the presence of osteoclastic giant cells (OGCs) in the stroma. The giant cells are generally associated with an inflammatory, fibroblastic, hypervascular stroma, with extravasated erythrocytes, lymphocytes, and monocytes, along with mononucleated and binucleated histiocytes, some containing

hemosiderin. The giant cells vary in size and contain a variable number of non-atypical nuclei. The carcinomatous part of the lesion is most frequently a well – to moderately differentiated infiltrating breast carcinoma NST but all the other histological types have been observed particularly invasive cribriform carcinoma, and also tubular, mucinous, papillary, lobular, squamous, and other metaplastic patterns and pleomorphic carcinoma.

Carcinoma with choriocarcinomatous features. The 2012 WHO classification defines these as NST carcinoma associated with elevated levels of serum human chorionic gonadotropin. Up to 60% of NST carcinomas have been found to contain HCG-positive cells. Histological evidence of choriocarcinomatous differentiation, however, is exceptionally rare with only a few cases reported.

Carcinoma with melanotic features. The 2012 WHO classification defines this as an exceptionally rare tumor which appears to represent combinations of NST carcinoma and malignant melanoma and in some of these cases exhibits a transition from one cell type to the other. The mere presence of melanin in breast cancer cells should not be construed as evidence of melanocytic differentiation, since pigmentation of carcinoma cells with melanin can occur when breast cancers invade the skin and involve the dermoepidermal junction. In addition, care must be taken to distinguish tumors showing melanocytic differentiation from breast carcinomas with prominent cytoplasmic deposition of lipofuscin. It should also be noted that most melanotic tumors of the breast represent metastases from malignant melanomas originating in extra-mammary sites. Primary melanomas may arise anywhere in the skin of the breast, but an origin in the nipple-areola complex is extremely rare.

Additional Classification Systems

Histological Grade

One of the most fundamental aspects of oncological pathology, which has undoubtedly stood the test of time, has been the recognition that the detailed morphological structure of tumors can be correlated with their degree of malignancy. Greenhough in 1928, in Boston, USA, undertook the first formal study of the grading of breast cancer. Scarff and his colleagues at the Middlesex Hospital in London re-examined Greenhough's method and decided that only three factors, tubule formation, nuclear pleomorphism, and hyperchromatism were of importance. Scarff's method has formed the basis of all subsequent grading systems. The perceived poor reproducibility and consistency has been largely resolved by use of semi objective scoring systems and adherence to written criteria. These studies have highlighted the need for grading to be carried out by trained histopathologists who work to an agreed protocol.

Invasive Carcinoma NST, Table 1 Semiquantitative method for assessing histological grade in breast carcinoma

Feature	Score
Tubule formation	
Majority of tumor (>75%)	1
Moderate degree (10–75%)	2
Little or none (<10%)	3
Nuclear pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic counts	
Dependent on microscope field area (see Table 2)	1–3

The Nottingham method, outlined in Tables 1 and 2, is the most widely used method. Three characteristics of the tumor are evaluated according to semi quantitative criteria, tubule formation as an expression of glandular differentiation, nuclear pleomorphism and mitotic counts. It has been validated through long term follow up of a large series of patients confirming conclusively the highly significant relationship between histological grade and prognosis; survival worsens with increasing grade (Elston and Ellis 1991). The method has now been shown to have good reproducibility in other centres and it has been adopted for use in the pathological data set of the United Kingdom NHS BSP and in the

Invasive Carcinoma NST, Table 2 Assignment of points for mitotic counts according to the field area

	Number of mitoses corresponding to		
Field diameter in mm	Score 1	Score 2	Score 3
0.40	Up to 4	5–8	9 or more
0.41	Up to 4	5–9	10 or more
0.42	Up to 4	5–9	10 or more
0.43	Up to 4	5–10	11 or more
0.44	Up to 5	6–10	11 or more
0.45	Up to 5	6–11	12 or more
0.46	Up to 5	6–11	12 or more
0.47	Up to 5	6–12	13 or more
0.48	Up to 6	7–12	13 or more
0.49	Up to 6	7–13	14 or more
0.50	Up to 6	7–13	14 or more
0.51	Up to 6	7–14	15 or more
0.52	Up to 7	8–14	15 or more
0.53	Up to 7	8–15	16 or more
0.54	Up to 7	8–16	17 or more
0.55	Up to 8	9–16	17 or more
0.56	Up to 8	9–17	18 or more
0.57	Up to 8	9–17	18 or more
0.58	Up to 9	10–18	19 or more
0.59	Up to 9	10–19	20 or more
0.60	Up to 9	10–19	20 or more
0.61	Up to 9	10–20	21 or more
0.62	Up to 10	11–21	22 or more
0.63	Up to 10	11–21	22 or more
0.64	Up to 11	12–22	23 or more
0.65	Up to 11	12–23	24 or more
0.66	Up to 11	12–24	25 or more
0.67	Up to 12	13–25	26 or more
0.68	Up to 12	13–25	26 or more
0.69	Up to 12	13–26	27 or more
0.70	Up to 13	14–27	28 or more

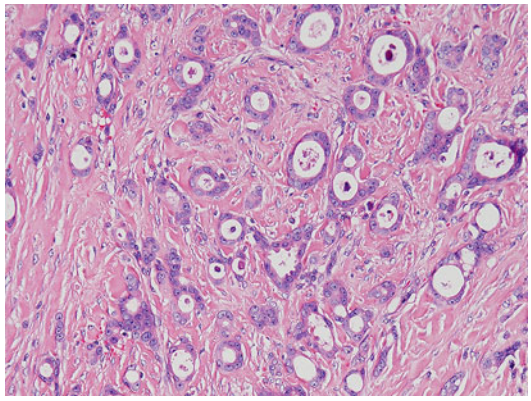
USA and Europe (Rakha et al. 2010). Examples of grade 1, grade 2, and grade 3 carcinomas are shown in Figs. 2a, b, 3, 4, and 5.

Tumor Infiltrating Lymphocytes

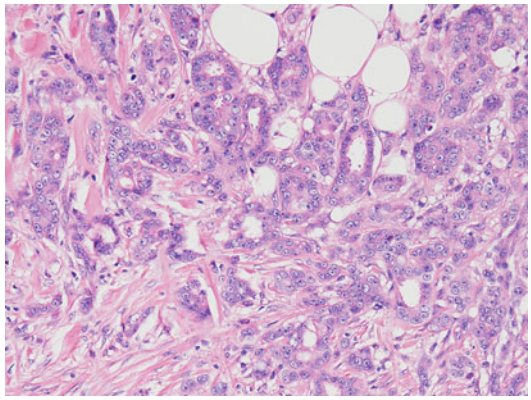
It has been recognized that some types of breast cancer such as medullary like, NST, triple negative and HER2 positive, are associated with tumor-infiltrating lymphocytes (TILs) (Fig. 6). Formal evaluation of TILs is gaining momentum as evidence strengthens for the clinical relevance of phenomenon which is regarded as an immunological biomarker. The extent of lymphocytic infiltration in tumor tissue can be assessed as by evaluation of hematoxylin and eosin (H&E)-stained tumor sections and has been shown to provide prognostic and potentially predictive value, particularly in the triple-negative and HER 2 positive settings.

A standardized methodology for evaluating TILs has been developed for visual assessment on H&E sections (Salgado et al. 2015) by the International TILs Working Group. Their key recommendations are:

1. TILs should be reported for the stromal compartment (=% stromal TILs).

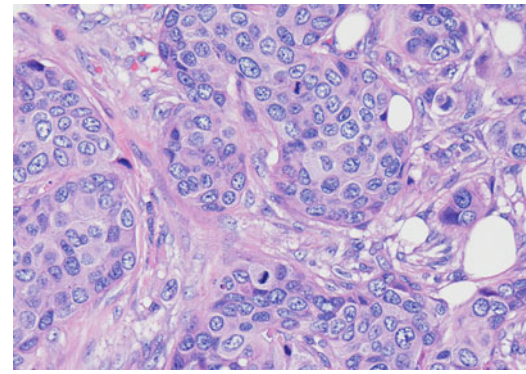


Invasive Carcinoma NST, Fig. 3 Example of a grade 1 carcinoma. The tumour shows prominent tubule/gland formation (score 1), moderate to high nuclear pleomorphism (score 3) and no mitotic figures (score 1). Final garde score 5 indicating a grade 1 invasive carcinoma. The differential diagnosis would be with a pure tubular carcinoma but the degree of nuclear pleomorphism exhibited preclude a diagnosis of pure tubular carcinoma and classification as grade 1 NST carcinoma is appropriate



Invasive Carcinoma NST, Fig. 4 Example of a grade 2 invasive carcinoma. There is over 10% tubule/gland formation, score 2, moderate nuclear pleomorphism, score 2 and on assessment of 10 calibrated high power fields a mitotic frequency score of 2. Total grade score 6, indicating a grade 2 tumor

2. TILs should be evaluated within the borders of the invasive tumor.
3. Exclude TILs outside of the tumor border and around DCIS and normal lobules.
4. Exclude TILs in tumor zones with crush artifacts, necrosis, regressive hyalinization as well as in the previous core biopsy site.

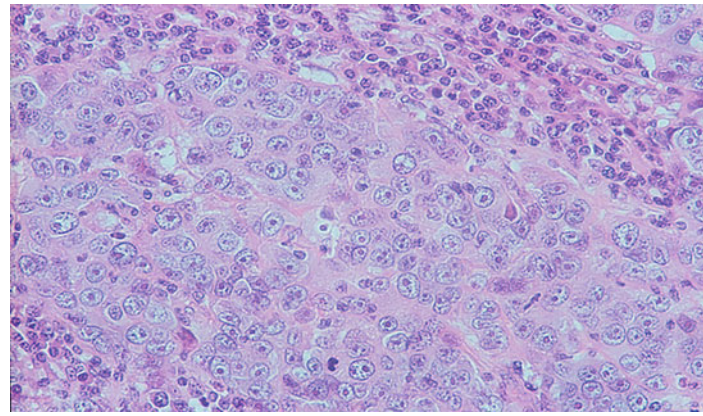


Invasive Carcinoma NST, Fig. 5 Example of a grade 3 tumor. There is no evidence of tubule/gland formation, score 3, a high degree of nuclear pleomorphism and increase in nuclei size, score 3, assessment of 10 calibrated high power fields showed a high frequency of mitosis, score 3. The total grade score is 9 indicating a grade 3 tumor

5. All mononuclear cells (including lymphocytes and plasma cells) should be scored, but polymorphonuclear leukocytes are excluded.
6. One section (4–5 μm, magnification ×200–400) per patient is currently considered to be sufficient.
7. Full sections are preferred over biopsies whenever possible.
8. A full assessment of average TILs in the tumor area by the pathologist should be used. Do not focus on hotspots.
9. TILs should be assessed as a continuous parameter.
10. No formal recommendation for a clinically relevant TIL threshold(s) can be given at this stage.

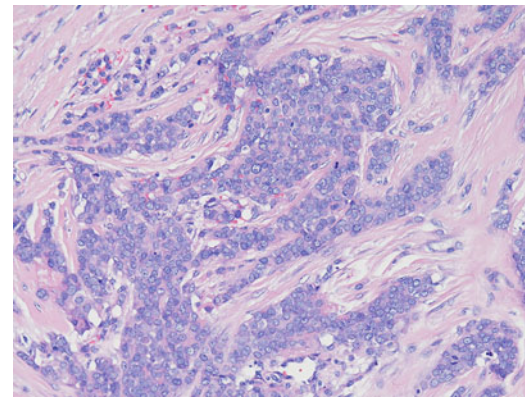
Immunophenotype

Being a heterogeneous form of breast cancer tumors of NST type have not distinct immunephenotypic characteristics. The majority of NST tumors are positive for GCDFP-15 and low molecular weight cytokeratin, including CK's 7, 8 and 18. All of the major gene expression molecular classes (luminal, basal/triple negative



Invasive Carcinoma NST, Fig. 6 A high grade invasive carcinoma with some medullary like features showing marked stromal infiltration by lymphocytes and plasma cells (TILs)

and HER2 positive) are represented in the NST group with the luminal ER positive tumors predominating, approximately 70–80% of NST breast cancers are ER-positive. The basal/triple negative for ER, progesterone receptor (PR) and HER2 group occur at a lower frequency (10–20%), as does the HER2 positive/ER positive and negative subgroups, with 12–20% of cases being HER2 positive.



Invasive Carcinoma NST, Fig. 7 An example of a triple negative, for ER, PR and HER2, grade 3 invasive carcinoma of NST type showing undifferentiated basal like characteristics

Molecular Features

NST breast cancer shows high genetic variation comparable to breast cancer as a whole. Historically breast cancer was regarded as a single disease with variable histology and clinical course. Recently high-throughput molecular biology analytical methods such as cDNA microarray analysis when applied to breast cancer as a whole and to the NST class revealed unexpectedly large-scale molecular differences between ER-positive cancers and ER-negative cancers (Fig. 7) (Allison 2012; Rakha and Green 2017). In addition these molecular biology studies have shown specific genetic lesions or regions of alteration associated with some histological special types or grade, for example the low nuclear grade tumors including invasive lobular (▶ Invasive Lobular Carcinoma) and tubular carcinoma (▶ Invasive Tubular Carcinoma) cluster in the luminal A intrinsic class and have distinct similar alterations of chromosomes 1 and 16. In contrast, the group of NST breast cancers harbors all the molecular intrinsic classes and has genetic alterations across the genome. These results imply that breast cancer overall and the NST group appear to develop via multiple different genetic evolutionary pathways. As a consequence, NST breast cancer is viewed not as a single disease but as a collection of several biologically distinct neoplastic diseases that arise from the breast epithelium.

All four different molecular types of breast cancer can be observed in NST breast cancer:

Luminal A type – low proliferation ER-positive
Luminal B type – highly proliferative ER-positive, PR low or negative

Basal/triple negative – ER/PR-negative and HER-2-negative
HER-2 amplified breast cancer

However, for clinical purposes, these have been further refined by the St Gallen consensus conference (Curigliano et al. 2017):

St Gallen 2017 division of subtypes

Clinical grouping	Notes[a]
Triple negative	Negative ER, PR and *HER2*
Hormone receptor-negative and *HER2*-positive	International guidelines
Hormone receptor-positive and *HER2*-positive	International guidelines
Hormone receptor-positive and *HER2*-negative	ER and/or PgR positive ≥1%
– a spectrum of ER+/HER2-negative	
High receptor, low proliferation, low grade (luminal A-like)	Multi-parameter molecular marker 'good' if available.[b] High ER/PR and clearly low Ki-67 or grade.
Intermediate	Multi-parameter molecular marker 'intermediate' if available. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
Low receptor, high proliferation, high grade (luminal B-like)	Multi-parameter molecular marker 'bad' if available. Lower ER/PR with clearly high Ki-67, histological grade 3.

[a]Basal like breast cancer and *HER2*-enriched subtype can be defined by genomic assay only.
[b]No role for gene testing in clinical pathologic low risk cases (pT1a, pT1b, G1, ER high, pN0).

Differential Diagnosis

The principle differential diagnosis relates to distinction from invasive mammary carcinomas of recognized pure special types such as invasive lobular carcinoma (▶ Invasive Lobular Carcinoma), tubular (▶ Invasive Tubular Carcinoma)/invasive cribriform carcinoma (▶ Invasive Cribriform Carcinoma), mucinous carcinoma (▶ Invasive Cribriform Carcinoma), medullary-like carcinoma (▶ Invasive Carcinoma with Medullary Features), and other rarer special types. Such distinction requires knowledge and application of the defining features of each type which are predominantly morphological and detailed elsewhere in the relevant sections. However, a very high proportion of invasive lobular carcinomas have alterations in the E-Cadherin gene with resultant loss of E-Cadherin protein expression. Immunohistochemical staining for E-Cadherin can therefore be a helpful supporting adjunct test to differentiate the lobular class from the NST group of cancers.

The UK, EU, and WHO classification systems highlight the need for >90% purity of special type characteristics to define most special types of cancer to ensure their prognostic characteristics will be manifest. Tumors exhibiting between 50% and 90% special type characteristics are recommended to be designated as mixed special and NST type (see above).

Tumors of unusual morphological appearance, particularly if ER negative and lacking an accompanying in situ component such as DCIS, may represent a metastatic tumor deposit in the breast rather than a primary NST mammary carcinoma. Clinical information relating to past medical history of a malignancy elsewhere, clinical investigation, and immunophenotype of the tumor can help distinguish a primary from a metastatic tumor (Lee 2007).

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