Invasive Carcinomas

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There are several histologic subtypes of invasive carcinoma of the breast, including, but not limited to the following: invasive carcinoma of no special type (commonly known as invasive ductal carcinoma); invasive lobular carcinoma; tubular carcinoma; carcinoma with medullary features (sometimes called medullary carcinoma); and metaplastic carcinoma. Invasive (or infiltrating) ductal carcinoma (IDC) accounts for the majority (approximately 75%) of breast cancers, with invasive lobular carcinoma (ILC) accounting for 5–15%. Ultimately, management and prognosis are based on size, grade, predictive marker status, molecular phenotype, tumor biology, nodal status, and distant metastasis.

More aggressive, rapidly growing high nuclear grade IDCs, often triple negative cancers, tend to be expansile, round, or oval masses on imaging, mimicking some benign masses. They may be dense radiographically with nearly circumscribed margins; sonographically they may be nearly anechoic but should not be

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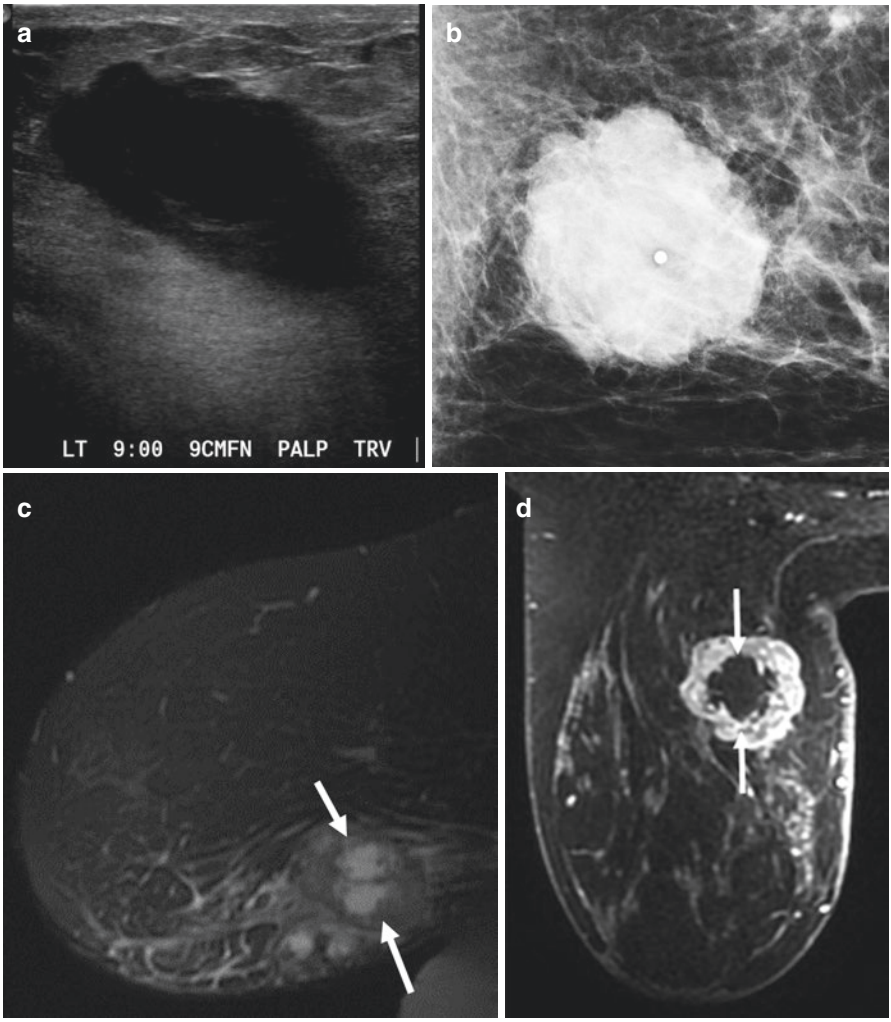


Fig. 9.1 Invasive ductal carcinoma, high nuclear grade. (**a**) Ultrasound shows a nearly anechoic, "cystic" appearing mass; however, its microlobulated borders and density mammographically (**b**) portend a more suspicious etiology in this 42-year-old woman. A metallic BB placed on the overlying skin indicates this is palpable to the patient. (**c**) Pre-contrast sagittal T2-weighted (fluid-sensitive) MRI image shows increased signal around the mass (peritumoral edema) and centrally in the mass (*between arrows*) that corresponds absence of enhancement on axial post-contrast imaging (**d**), reflecting central necrosis

mistaken for a cyst (Fig. 9.1). On MRI, these masses may demonstrate heterogeneous or peripheral enhancement, sometimes with central nonenhancement and T2 hyperintensity ("fluid" signal) that may reflect central necrosis, and peritumoral edema. In contrast, low nuclear grade IDCs more commonly present as ill-defined masses with spiculated margins or architectural distortion; the spicules

are indicative of its slower, more infiltrative growth pattern, "creeping" along tissue planes and disrupting ligaments (Fig. 9.2). Some of the "mass" on imaging may be part of a fibrotic or a desmoplastic reaction, rather than viable tumor. While low-grade carcinomas enhance on MRI, contrast uptake may be non-mass (i.e., it does not conform to the definition of a mass; it may be a "region" of enhancement) in appearance and less avid than that of a higher-grade tumor. Malignant-type calcifications seen radiographically in association with a mass suspicious for IDC may reflect associated ductal carcinoma in situ; these may extend a distance away from the mass such that additional biopsy may be needed

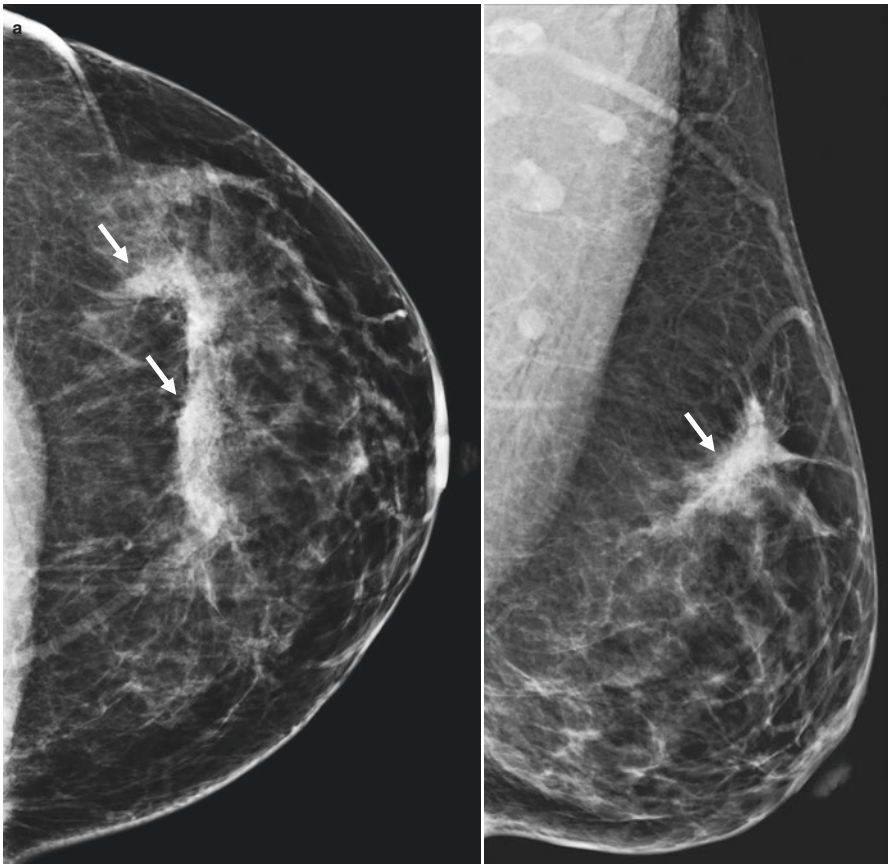


Fig. 9.2 Invasive ductal carcinoma, low nuclear grade. (**a**) Screening mammogram in this 41-year-old woman shows architectural distortion (*arrows*) in the upper central aspect of the left breast—"straightening" of the parenchymal lines. (**b**) On ultrasound of the upper inner and outer quadrants, multiple areas of ill-defined hypoechogenicity and disruption of tissue planes are seen, without an expansile mass. (**c**) Post-contrast axial MRI image demonstrates non-mass enhancement occupying the majority of the parenchyma in the upper quadrants (*arrow*); the normal right breast is shown for comparison

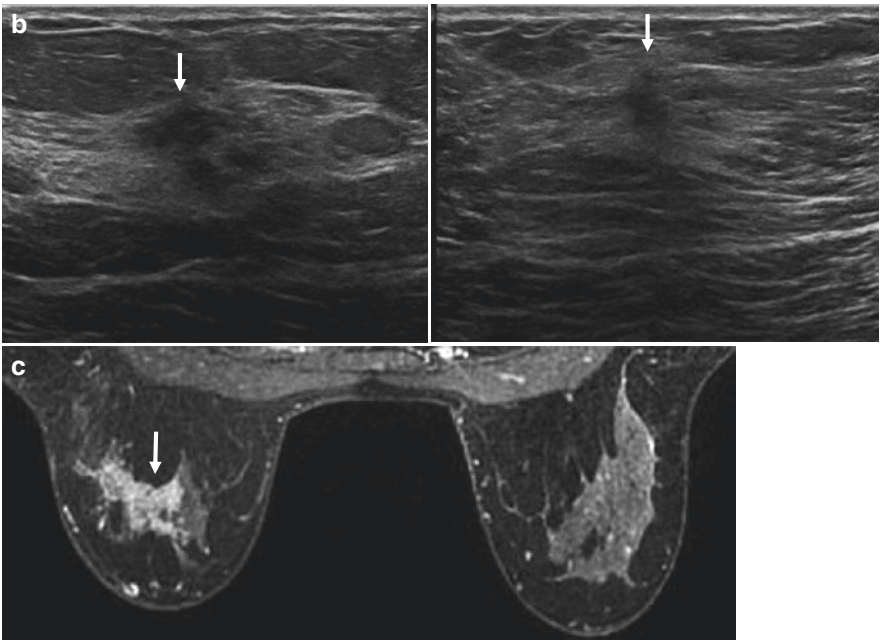


Fig. 9.2 (continued)

to confirm extent of disease for surgical planning (malignant-type calcifications themselves are not seen on MRI).

Mucinous and papillary carcinomas, seen more commonly in postmenopausal women, are less aggressive and metastasize less frequently than IDC, providing for a better prognosis. This may seem counterintuitive as these masses are classically described as "large" and expansile; however, their size comes from their internal matrix. On imaging, these are typically round or oval lobulated masses, and their echogenicity can help predict their histology (Figs. 9.3 and 9.4). Mucinous carcinomas tend to be iso- to slightly hyperechoic and are slow growing. Papillary carcinomas are typically complex solid and cystic and may grow more rapidly depending in part on the cystic component but may also be spiculated and solid. The mucin and fluid in these masses, respectively, also contribute to T2 hyperintensity (fluid signal) on MRI. Additionally, non-enhancing septa may be seen in mucinous cancers, compared with the enhancing solid portions of the vascular papillary carcinoma. Although these may present as large masses, the imaging features should supersede size when trying to confirm radiologic-pathologic concordance; all cancers have a starting point and may be found in early stages when still small. Papillary carcinomas are further described in the chapter "Papillary Lesions." Tubular carcinomas tend to be small (< 1 cm) masses with spiculated margins, or areas of distortion, and are also slow growing. Histologically they may be associated with radial scars or complex sclerosing lesions, which is why excision is recommended for these high-risk lesions if found on imaging-guided core biopsy.

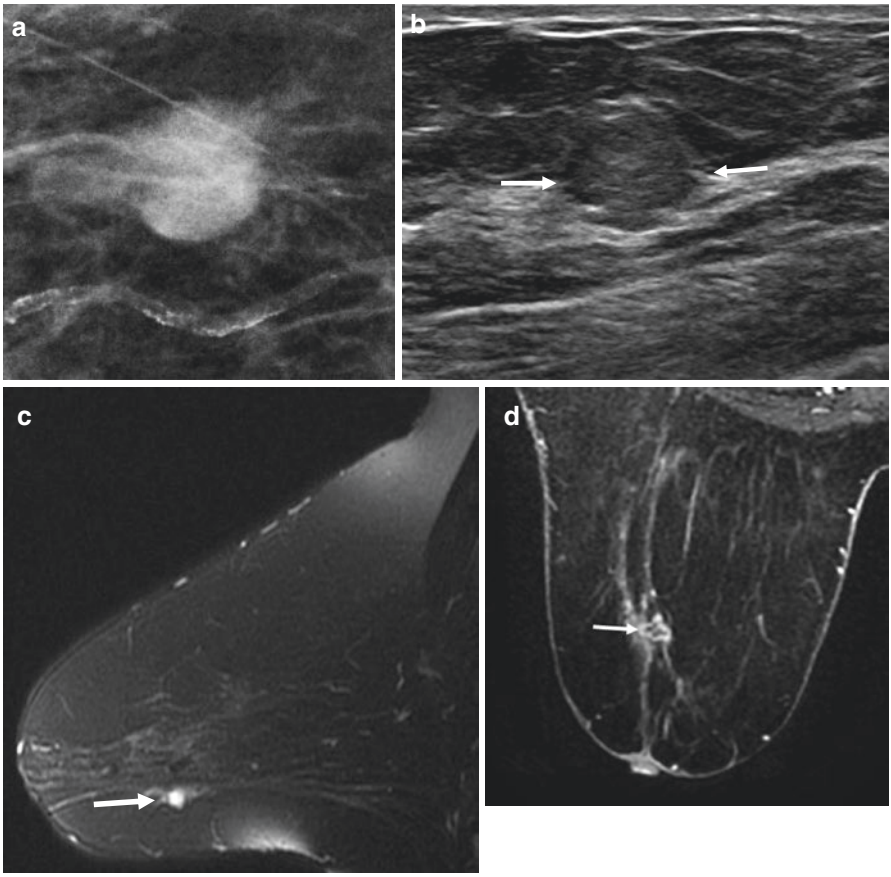


Fig. 9.3 Mucinous carcinoma in an 80-year-old woman. (**a**) Spot compression view after screening callback shows a round equal-density mass with mostly circumscribed and some indistinct margins. (**b**) On ultrasound this was an iso- to slightly hyperechoic mass (*between arrows*), relative to subcutaneous fat. (**c**) Pre-contrast sagittal T2-weighted (fluid-sensitive) MRI image shows a mass of increased signal intensity (*arrow*) that corresponds to a peripherally enhancing mass on post-contrast images. (**d**) The central portion of the mass is mucin, which itself does not enhance

Metaplastic carcinomas are rapidly growing masses with a worse prognosis, with axillary or distant (including hematogenous) metastases possible at the time of diagnosis (Fig. 9.5). By imaging they may be indistinguishable from a high nuclear grade IDC NOS, but histologically they are comprised of glandular, squamous or mesenchymal elements.

Invasive lobular carcinoma (ILC), which represents about 10% of all breast cancers, is more common in postmenopausal women and is slow growing. Radiographically, ILC may appear as an area of architectural distortion,

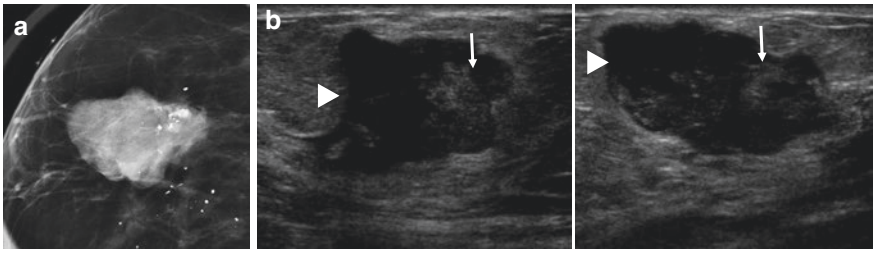


Fig. 9.4 Papillary carcinoma in an 84-year-old woman. (**a**) Spot tangential mammographic view shows an equal-density oval mass with circumscribed and lobulated margins and associated and adjacent coarse calcifications. (**b**) Orthogonal ultrasound images demonstrate a complex solid (*arrows*) and cystic (*arrowheads*) mass. The solid portion was targeted for ultrasound-guided needle biopsy. Although at core biopsy a papillary lesion with involvement by ductal carcinoma in situ was identified, invasive disease was found at lumpectomy. Intraductal and invasive papillary carcinoma may be indistinguishable on imaging

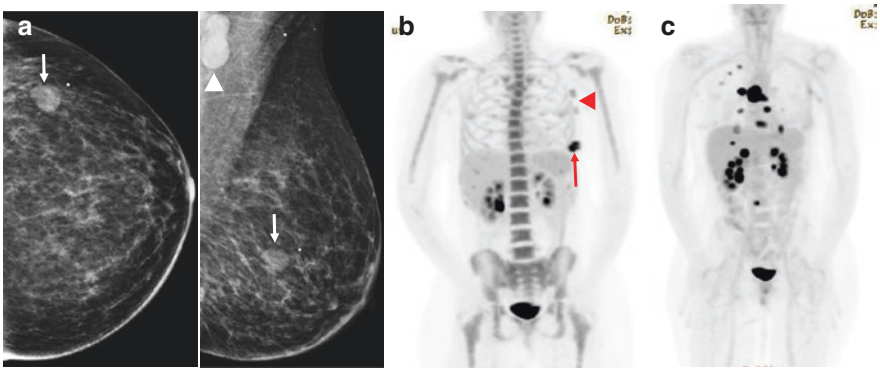


Fig. 9.5 Metaplastic carcinoma. (**a**) A 50-year-old woman presenting with a palpable mass in the outer central aspect of the left breast (*arrows*) and palpable axillary adenopathy (*arrowhead*). (**b**) 3-D maximum intensity projection reconstructions from a PET/CT scan show persistent disease in the breast (*arrow*) and to a lesser degree in the axilla (*arrowhead*) 7 months into chemotherapy and (**c**) progression of metastases at 11 months despite mastectomy, axillary dissection, and additional chemotherapy

developing asymmetry, or mass with spiculated margins, rather than an expansile mass, alluding to its more indolent, "single-file" cell growth pattern. Also because of its histology, ILC may be planar, seen better in one plane (classically the craniocaudal projection) than the orthogonal. Sonographically, these may be quite ill-defined masses with disruption of tissue planes and intense posterior acoustic shadowing, or vague areas of architectural distortion (Fig. 9.6). One uncommon exception is pleomorphic ILC, an aggressive subtype that manifests as an expansile mass, and is treated like a high nuclear grade IDC (Fig. 9.7). ILC may also present with diffuse changes (edema) in the background of an enlarging or shrinking breast.

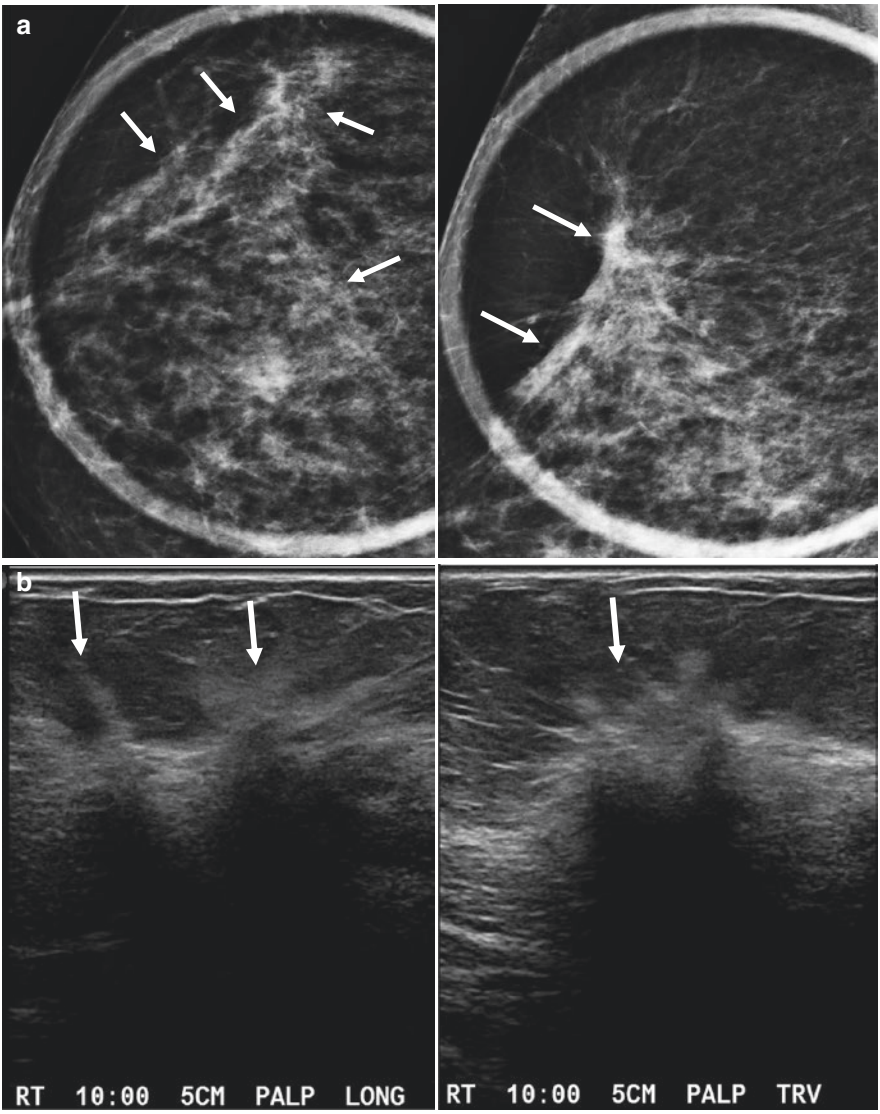


Fig. 9.6 Invasive lobular carcinoma. (**a**) Spot compression CC and MLO views done in a 68-year-old woman recalled from a screening mammogram show architectural distortion, "straightening" of the parenchymal lines (*arrows*). (**b**) Sonographically, ill-defined hypoechoic to nearly anechoic tissue with echogenic peaks (*arrows*) that disrupt tissue planes, and posterior acoustic shadowing, all confirmed in orthogonal planes, reflects the distortion seen radiographically

In patients in whom a suspicious mass is seen mammographically, sonography allows for further characterization and biopsy guidance, as well as the opportunity to evaluate the axilla for evidence of lymph node metastasis. As with calcifications, biopsy of the mass can be done with a needle under imaging

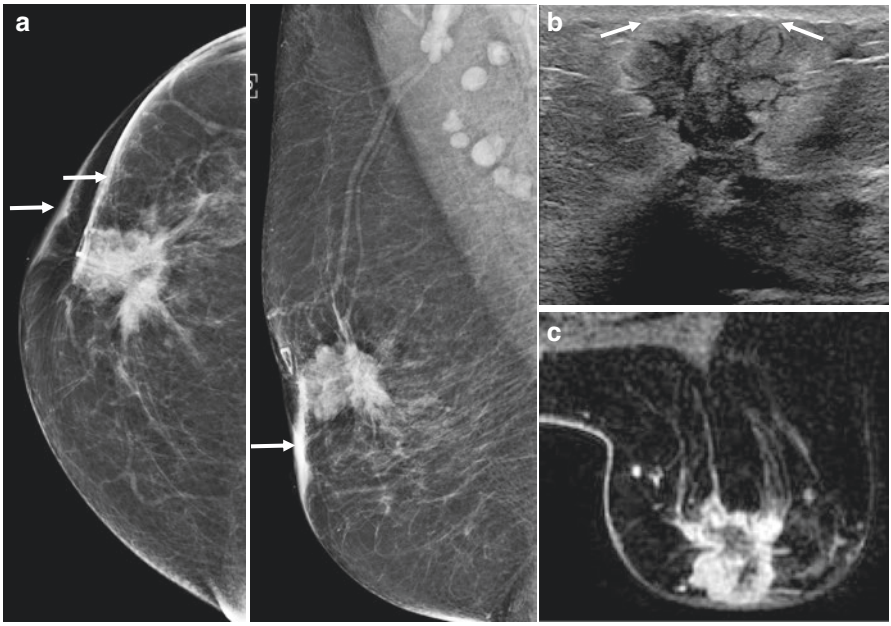


Fig. 9.7 Invasive lobular carcinoma, pleomorphic type. (**a**) Diagnostic mammogram in a 65-year-old woman with a "lump." There is skin thickening and retraction overlying the mass (*arrows*). (**b**) Skin involvement is confirmed on ultrasound, as this heterogeneous mass is inseparable from the deep dermal layer (*arrows*). (**c**) Post-contrast axial MRI image showing an irregular mass with thick rim enhancement extending to the skin. Lobular carcinoma rarely presents as an expansile mass, except for this aggressive subtype that clinically mimics a grade 3 invasive ductal carcinoma

guidance, or surgically. However, the former is preferred in the majority of cases as it is far less invasive, does not require sedation or special patient preparation (e.g., withholding of anticoagulation), costs less, and can allow for appropriate staging and surgical planning prior to definitive treatment. A metallic clip placed in the mass at the time of biopsy is most useful if the treatment plan includes neoadjuvant chemotherapy that will shrink the lesion to the point that it is occult on preoperative imaging or wire/seed localization; in our experience, in patients in whom lumpectomy (partial or segmental mastectomy) is a first-line treatment because of smaller lesion size (or patient preference), the tumor is still visible on imaging for preoperative localization on or shortly before the day of surgery regardless of a clip. Ultrasound-guided core-needle biopsy (or fine needle aspiration) of axillary adenopathy can be also done in the same setting as for the primary breast mass, providing the surgeon and oncologist additional information with regard to staging. A positive lymph node can also be

marked with a clip so that surgical excision can be confirmed with a specimen radiograph.

Once a diagnosis of breast cancer is confirmed by imaging-guided core-needle biopsy, MRI may be used to evaluate the extent of disease to aid in treatment planning. The sensitivity of MRI is higher than that of mammography or ultrasound, some reporting as high as 100% for invasive cancer, and the cancer detection rate is nearly double that of mammography and ultrasound combined, resulting in detection of additional disease that changes management in up to 20% of patients, most commonly shifting from breast-conserving treatment (BCT; lumpectomy and radiation) to mastectomy. This includes finding multifocal or multicentric disease in up to 10–25% and contralateral disease in up to 6%. However, the use of MRI remains controversial because there is also data showing that this test does not significantly improve re-excision or local recurrence rates, suggesting that surgical planning is adequately guided by mammography and ultrasound and that any "undetected" or residual disease after lumpectomy may be treated by subsequent breast radiation and systemic adjuvant chemotherapy without negatively impacting survival. Moreover, by current data, the conversion rate of lumpectomy to mastectomy based on additional MRI findings seems to outnumber the recurrence rates in patients who undergo BCT without a preoperative MRI. Therefore, some have suggested that the additional MRI findings may not lead to future "biologically significant" disease.

These arguments are somewhat counterintuitive for many reasons encountered in day to day practice, one being the principle of confirming the extent of disease suspected on routine imaging, namely, mammographically or sonographically. For example, if a patient has several centimeters of segmentally distributed suspicious calcifications, the accepted practice is to biopsy 2 sites, the two extremes in terms of location, that are far enough away from each other to "prove" that all of the involved and intervening tissue must be resected. Or if multiple separate, suspicious masses are seen on sonography, biopsy of more than 1 is typically done to prove multifocal or multicentric disease, and guide excision, if a patient desires breast conservation treatment. So if we are actively seeking out and biopsying additional disease to develop a complete, definitive treatment plan, one could argue that an MRI, which is more sensitive, is in keeping with this practice of establishing extent of disease. Many use the aforementioned argument that MRI-detected disease is not biologically significant; however, one could also counter that MRI-detected disease *is* biologically significant because its detection relies on properties unique to cancer: neovascularity and vascular permeability (tumor characteristics that result in the rapid, avid uptake of contrast). Iaconni et al. reported that MRI-detected multicentric disease was invasive in 76% of their

studied patients, and larger than 1 cm or the index cancer in up to 25%, suggesting biological relevance.

Moreover, patients are routinely taken back to the operating room for re-excision in the case of positive surgical margins, regardless of the use of preoperative MRI. If the disease potentially "left behind" that would be found by MRI is of no consequence, treated effectively with radiation and chemotherapy, at no detriment to survival, why incur the additional cost, risk, and recovery of another surgery for re-excision of disease "left behind" in the setting of positive margins?

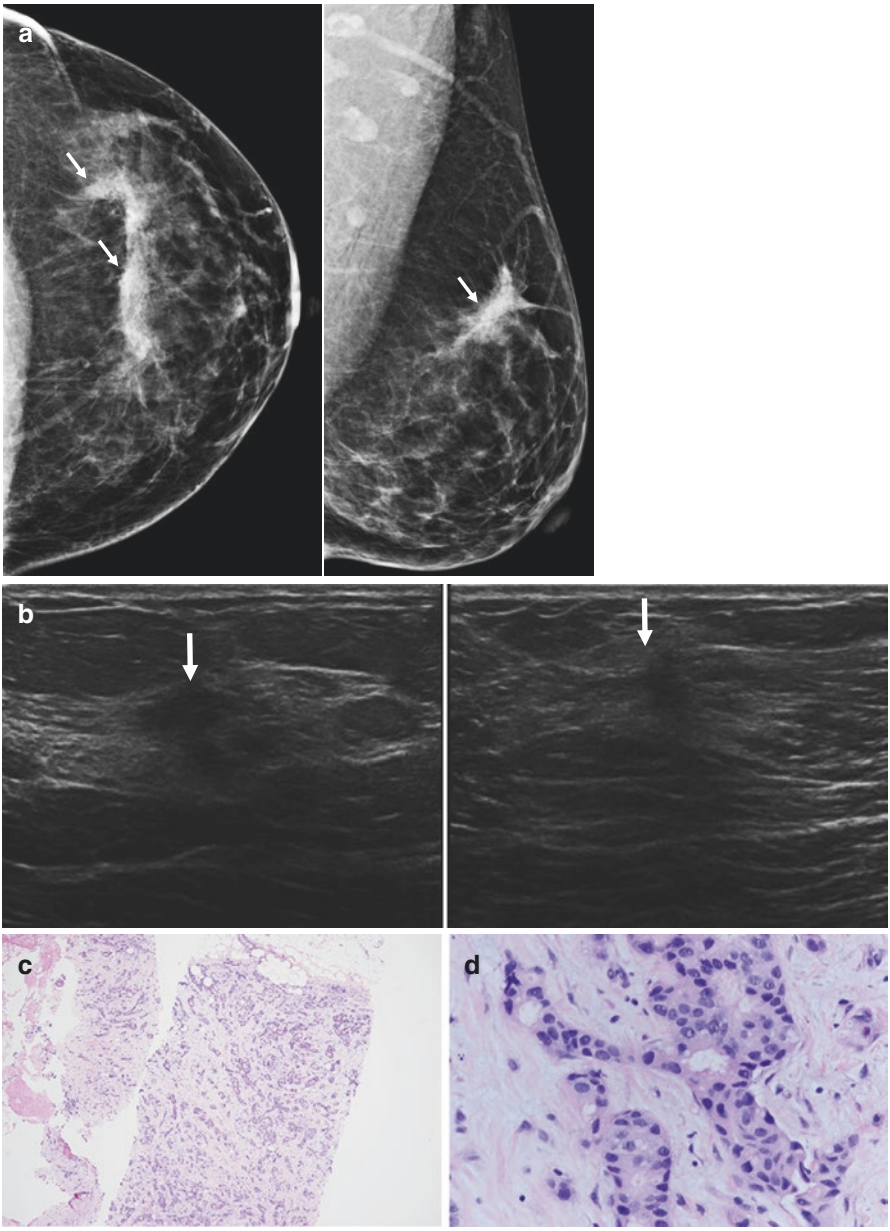
In this vein, surgical practices and breast-conserving treatment plans are evolving, such as more precise excisions with smaller volumes (margins) of tissue removed, multiple lumpectomies for multicentric disease (previously, multicentric disease was a contraindication to BCS), advanced oncoplastic reconstructive techniques, accelerated partial breast irradiation (versus whole breast irradiation), and use of recurrence risk assessment scores that may obviate the need for adjuvant chemotherapy. Therefore, the case could be made for using the most sensitive methods to accurately measure disease burden and exclude other sites of cancer preoperatively, thereby allowing for a more precise, patient-specific treatment plan before definitive surgery. Needless to say, these issues do not address the impact of preoperative MRI on detection of contralateral disease that could be treated simultaneously as the index lesion.

To address some of the controversies and conflicting data, at this time a multicenter, randomized controlled trial is in place to determine the effect of preoperative MRI with regard to staging and local regional control, with attention also on cost-effectiveness, quality of life, re-excision rates, and disease-free survival, among many other objectives.

In the meantime, in practice, while some advocate breast MRI should be done in all newly diagnosed patients, practice variations (and preferences of patients, surgeons, and oncologists) may focus efforts for MRIs in patients with cancer who are high risk, have dense breast tissue, and have triple negative disease or DCIS (given that it can be discontinuous and uncalcified), or ILC (which, due to its ill-defined appearance, can be underestimated with regard to size even on ultrasound and can have up to 30% risk of synchronous or contralateral disease). Additional suspicious lesions found on MRI should be worked up with a biopsy to help determine if the patient is still a candidate for breast conservation treatment.

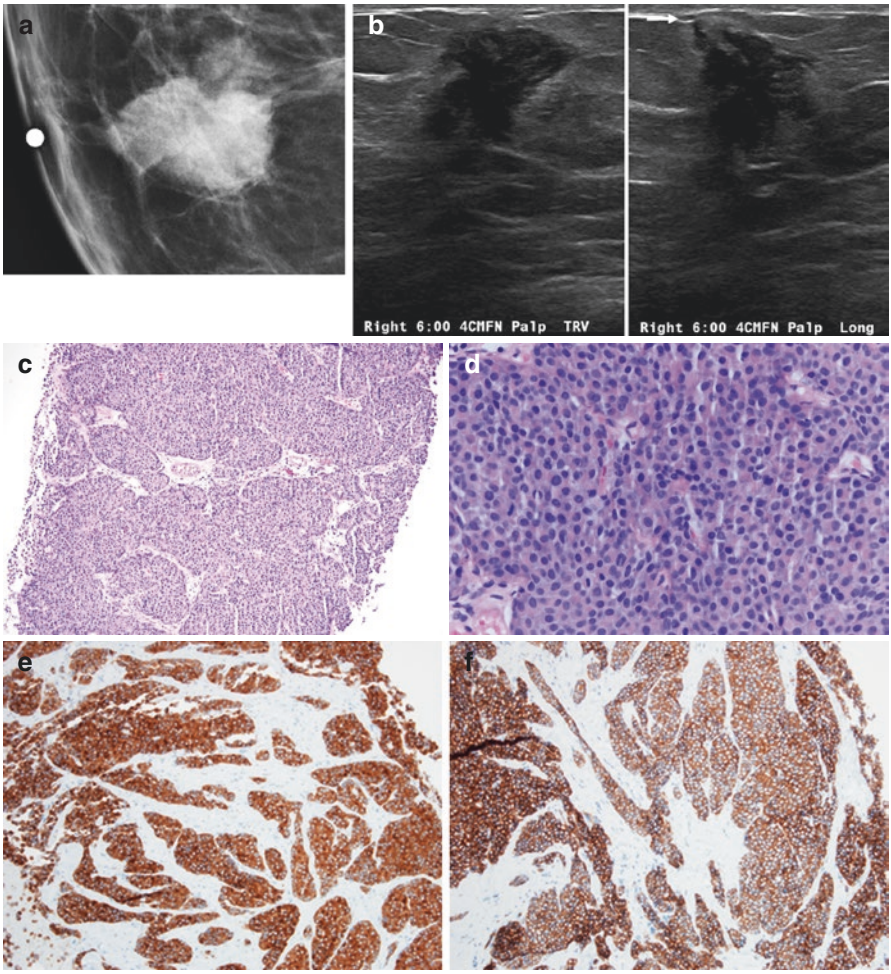
Chapter 2 of this text contains some discussion on the pathology approach to diagnosis of invasive carcinomas. All invasive carcinomas of the breast must be staged based on the most current AJCC Cancer Staging Manual. Selected radiologic-pathologic correlation of invasive carcinomas is highlighted below.

Case 1



Invasive ductal carcinoma, low nuclear grade. (**a**) Screening mammogram in a 41-year-old woman shows architectural distortion (*arrows*) in the upper central aspect of the left breast—"straightening" of the parenchymal lines. (**b**) On ultrasound of the upper inner and outer quadrants, multiple areas of ill-defined hypoechogenicity and disruption of tissue planes are seen, without an expansile mass. (**c**) Invasive ductal carcinoma. Epithelial cells in nests, cords, and tubules infiltrate a desmoplastic stroma. (**d**) The low-grade nuclei show minimal pleomorphism and uniform chromatin

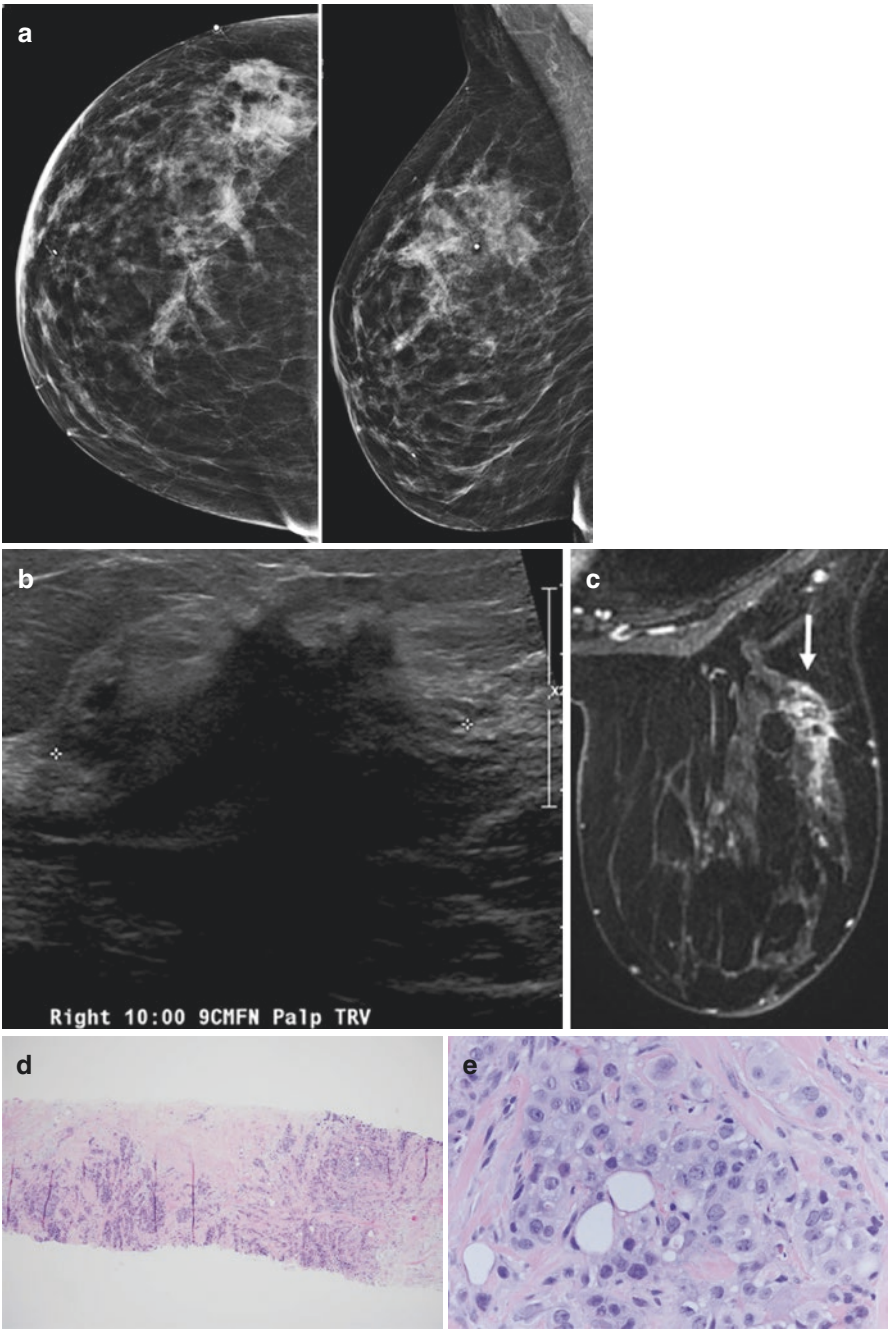
Case 2



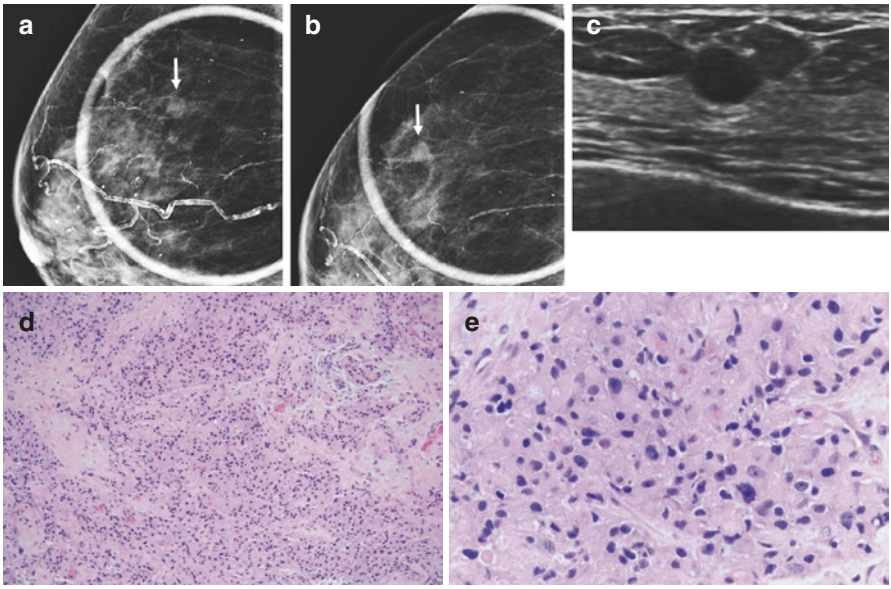
Invasive ductal carcinoma, low nuclear grade with neuroendocrine differentiation. (**a**) Spot tangential view of a palpable "lump" (marked on skin with a metallic BB) in a 62-year-old woman. The mass is irregular, with high density and with indistinct and spiculated margins. (**b**) Orthogonal ultrasound images show similar features. In addition, there is disruption of normal tissue planes and the mass approaches the skin (*arrow*). (**c** and **d**) Core-needle biopsy with infiltrating cells in solid nests/insular pattern with focal peripheral palisading, low nuclear grade, and fine chromatin. Necrosis is not identified. (**e**) The cells are diffusely positive for synaptophysin. (**f**) Expression of E-cadherin is preserved. The p63 stain was negative (*not pictured*)

Invasive ductal carcinoma, high nuclear grade. (**a**) A 54-year-old woman with a palpable (designated by metallic BB) nodular asymmetry in the upper outer quadrant of the right breast, which corresponds to an irregular, nearly anechoic but solid mass with angular and indistinct margins on ultrasound (**b**) and an irregular mass with heterogeneous enhancement on MRI (**c**, *arrow*). (**d**) Epithelial cells in small solid nests and cords infiltrate the desmoplastic stroma. (**e**) The high grade nuclei show pleomorphism and visible nucleoli

Case 3



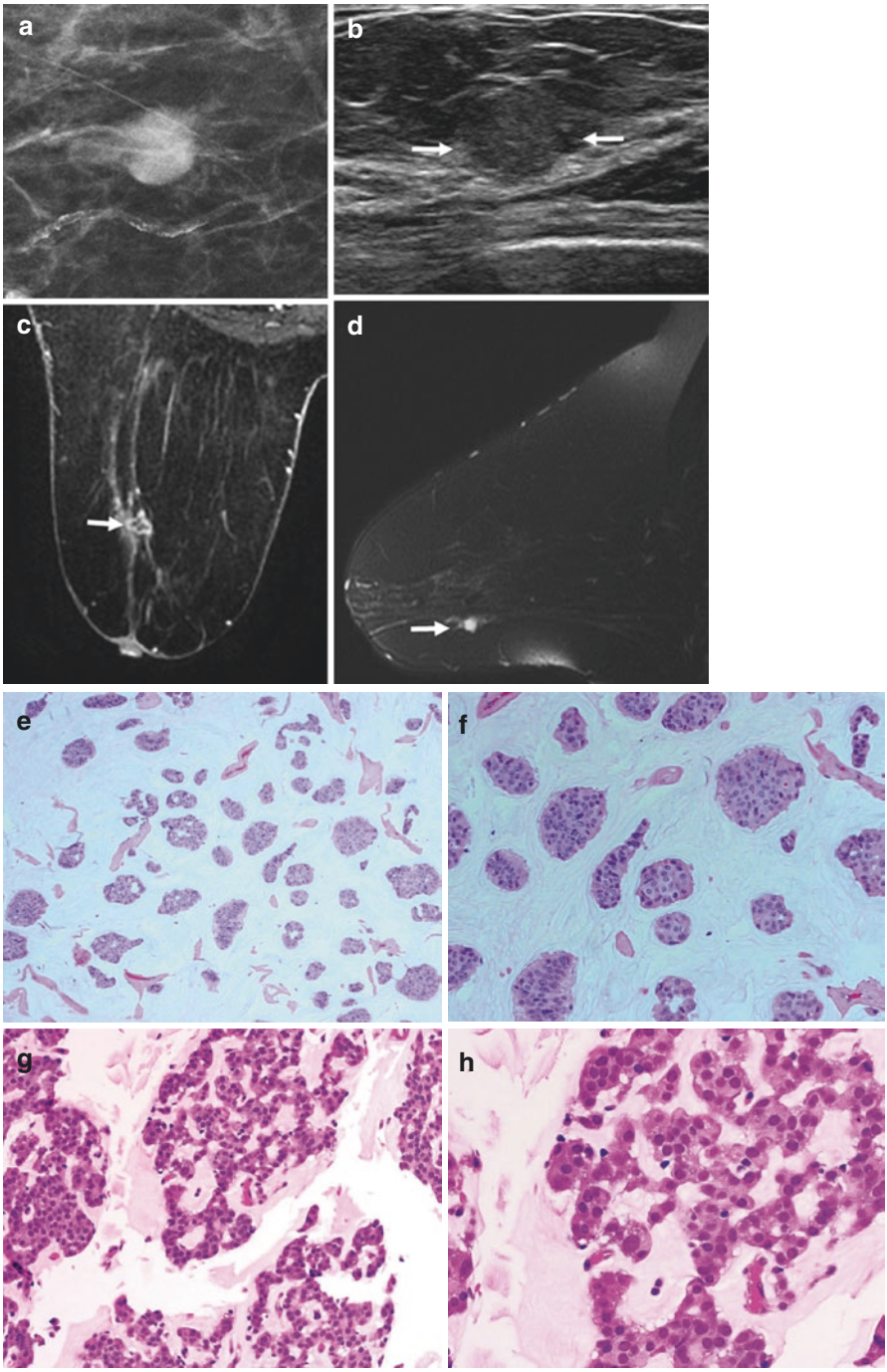
Case 4



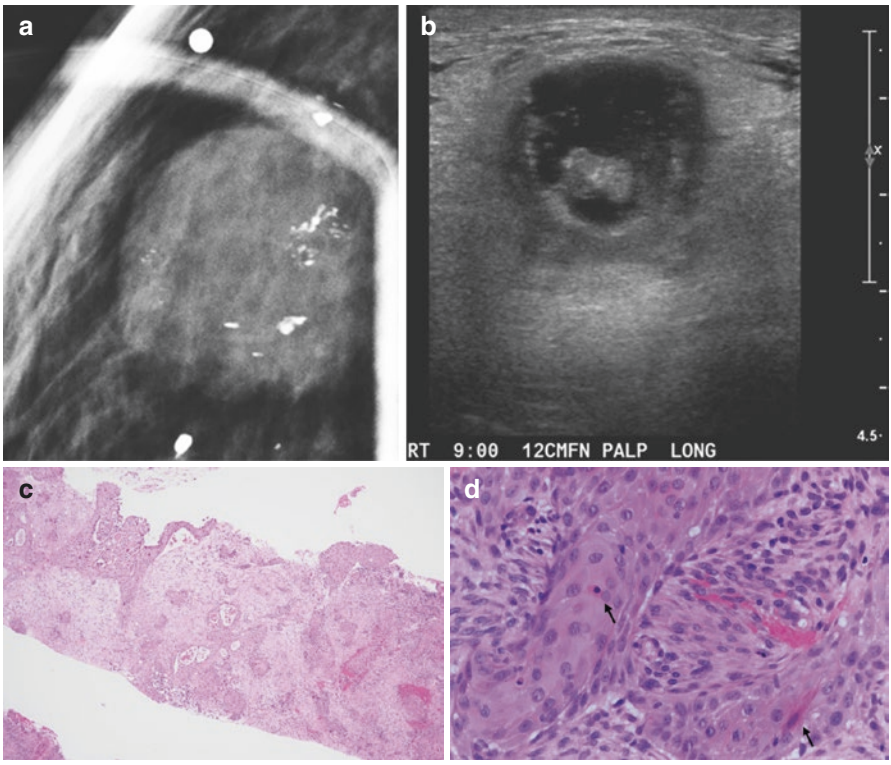
Invasive ductal carcinoma, intermediate nuclear grade with apocrine features. (**a**) CC and (**b**) MLO spot compression views of a mass (*arrow*) in the right breast in a 62-year-old woman with known locally advanced left breast cancer (not shown). (**c**) Targeted ultrasound shows a nearly anechoic mass. Because it is not clearly a cyst, biopsy is done. (**d** and **e**) Note the cells with abundant granular, eosinophilic cytoplasm, and mildly pleomorphic round nuclei with prominent nucleoli

Invasive ductal carcinoma, intermediate nuclear grade, with mucinous features/mucinous carcinoma. (**a**) An 80-year-old woman with a history of right lumpectomy and radiation for breast cancer, with new subcentimeter round mass with partially circumscribed and indistinct margins found in the left breast on annual mammogram. (**b**) Targeted ultrasound shows an isoechoic to slightly hyperechoic mass (*between arrows*) with circumscribed margins. (**c**) Central nonenhancement on the MRI with corresponding increased T2 (fluid) signal (**d**) reflects mucin (*arrows*). (**e** and **f**) Core-needle biopsies show nests of epithelial cells in pool of extracellular mucin, consistent with mucinous carcinoma. (**g** and **h**) Mucinous carcinoma in the excision specimen shows epithelial cells in in pool of extracellular mucin. A pure mucinous carcinoma must composed of more than 90% mucinous carcinoma, making the diagnosis difficult sometimes on core needle biopsy as the entire lesion is cannot be evaluated

Case 5

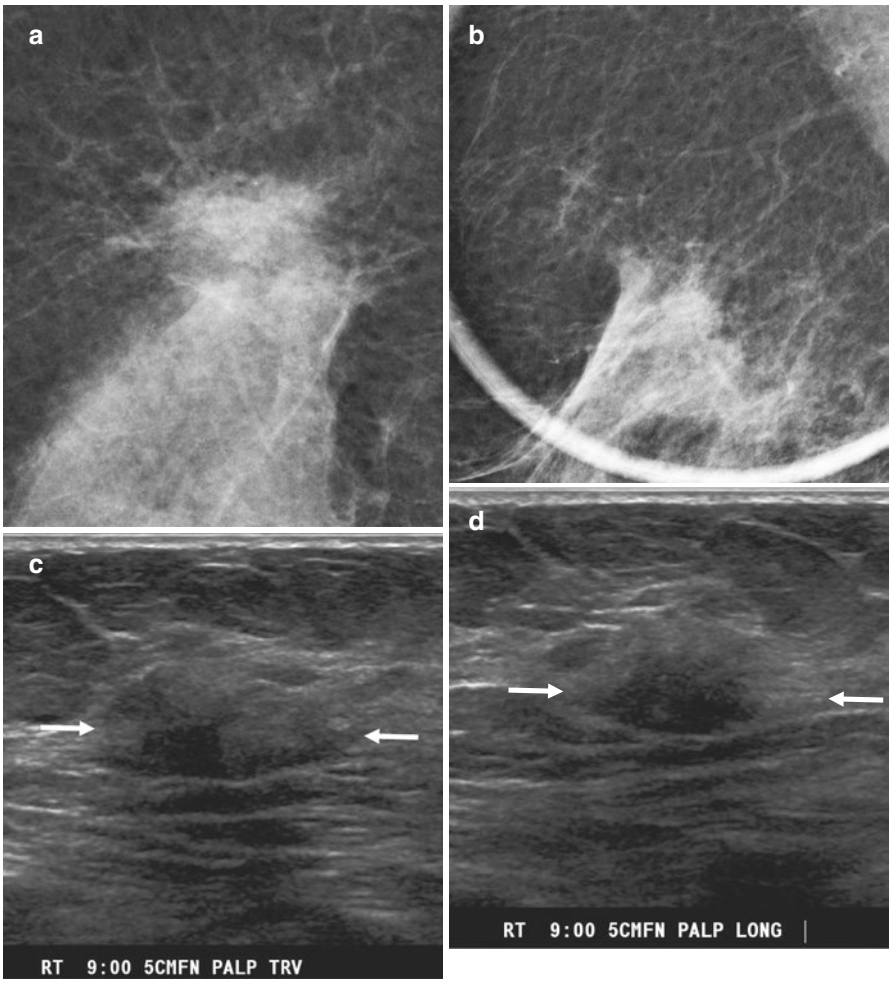


Case 6

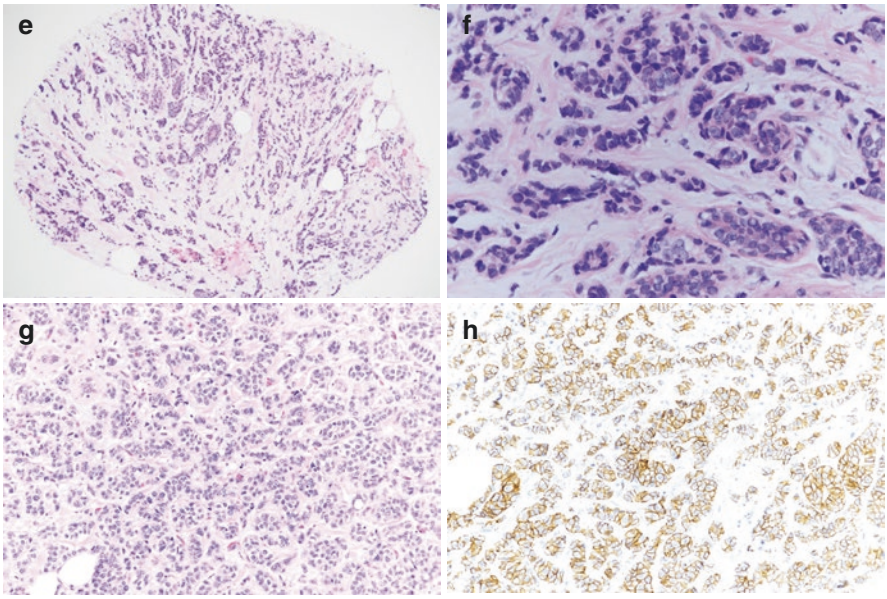


Invasive carcinoma with squamous features. (**a**) A palpable mass with mostly circumscribed margins and coarse calcifications is marked with an overlying metallic BB in this 87-year-old woman. (**b**) Complex solid and cystic mass is seen sonographically; ultrasound-guided biopsy targeted the solid (*deeper*) portion. (**c** and **d**) Invasive carcinoma shows extensive squamous features. This is a variant of metaplastic carcinoma

Case 7



Invasive ductal carcinoma, with lobular features. (**a** and **b**) CC and MLO spot compression views of a screening detected mass in a 64-year-old woman. The irregular mass is developing at the edge of the parenchyma in the right breast and has spiculated margins. (**c** and **d**) Orthogonal ultrasound images confirm an irregular mass (*arrows*) with indistinct margins and heterogeneous echogenicity and that disrupts tissue planes. (**e** and **f**) Core-needle biopsies show invasive carcinoma, with cells infiltrating as nests, as well as individual cells in linear distribution. (**g**) Similar histological features are seen in the excision specimen. (**h**) The e-cadherin stain is diffusely positive, arguing against invasive lobular carcinoma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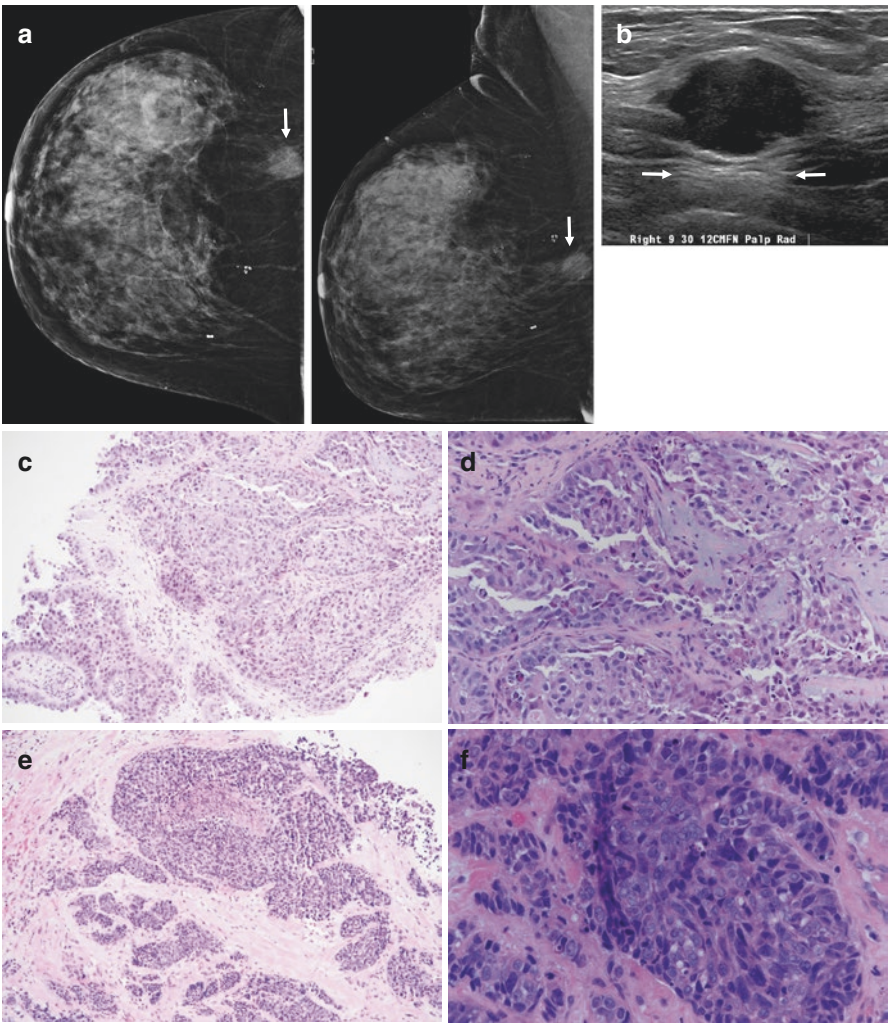
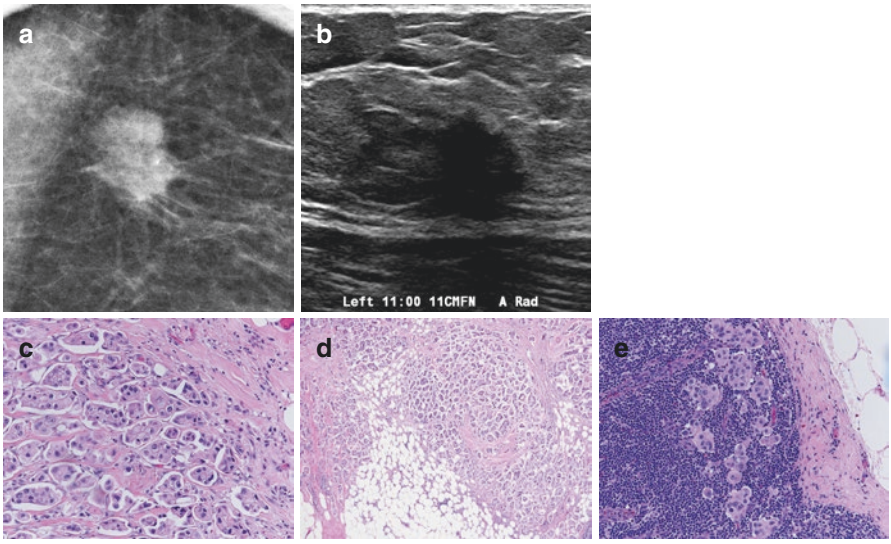
Case 8



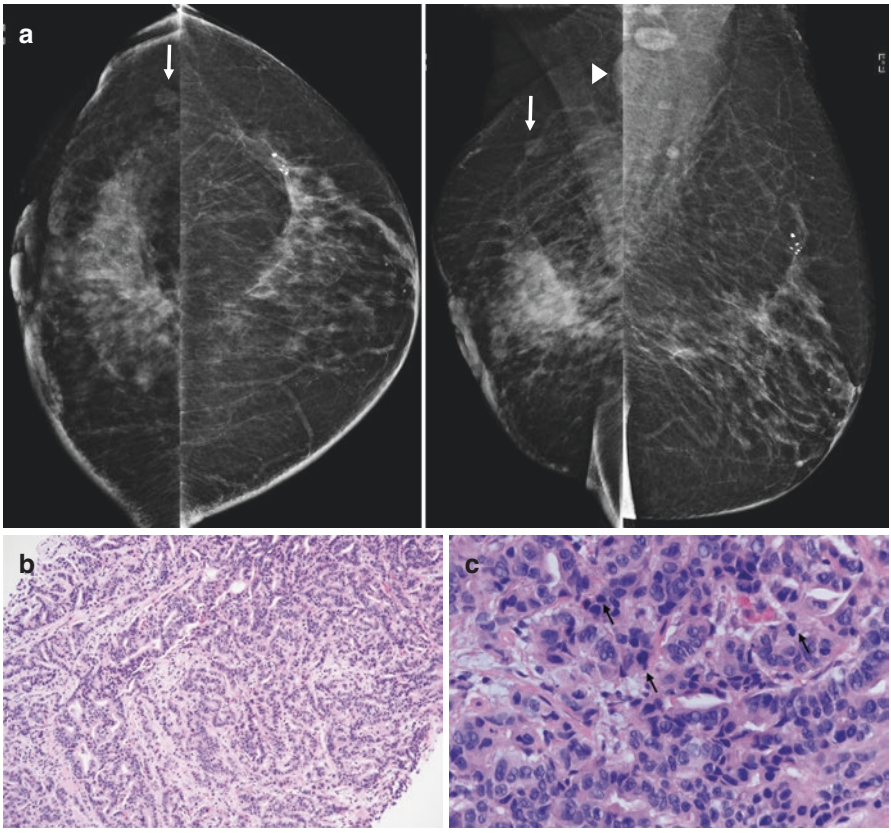
Invasive ductal carcinoma, high nuclear grade. (**a**) A 65-year-old woman with a round mass (*arrows*) in the retroglandular fat detected on screening mammogram. (**b**) Ultrasound shows an irregular, hypoechoic mass with mostly circumscribed and few indistinct margins. Posterior acoustic enhancement (*between arrows*) is nonspecific; this should not be mistaken for a complicated cyst. (**c** and **d**) Core biopsy: invasive ductal carcinoma, high nuclear grade, with papillary architecture. (**e** and **f**) Histologic variant of IDC, high nuclear grade with invasive ductal carcinoma consisting of solid nests of tumor cells with pleomorphic nuclei with coarse chromatin and prominent nucleoli

Case 9



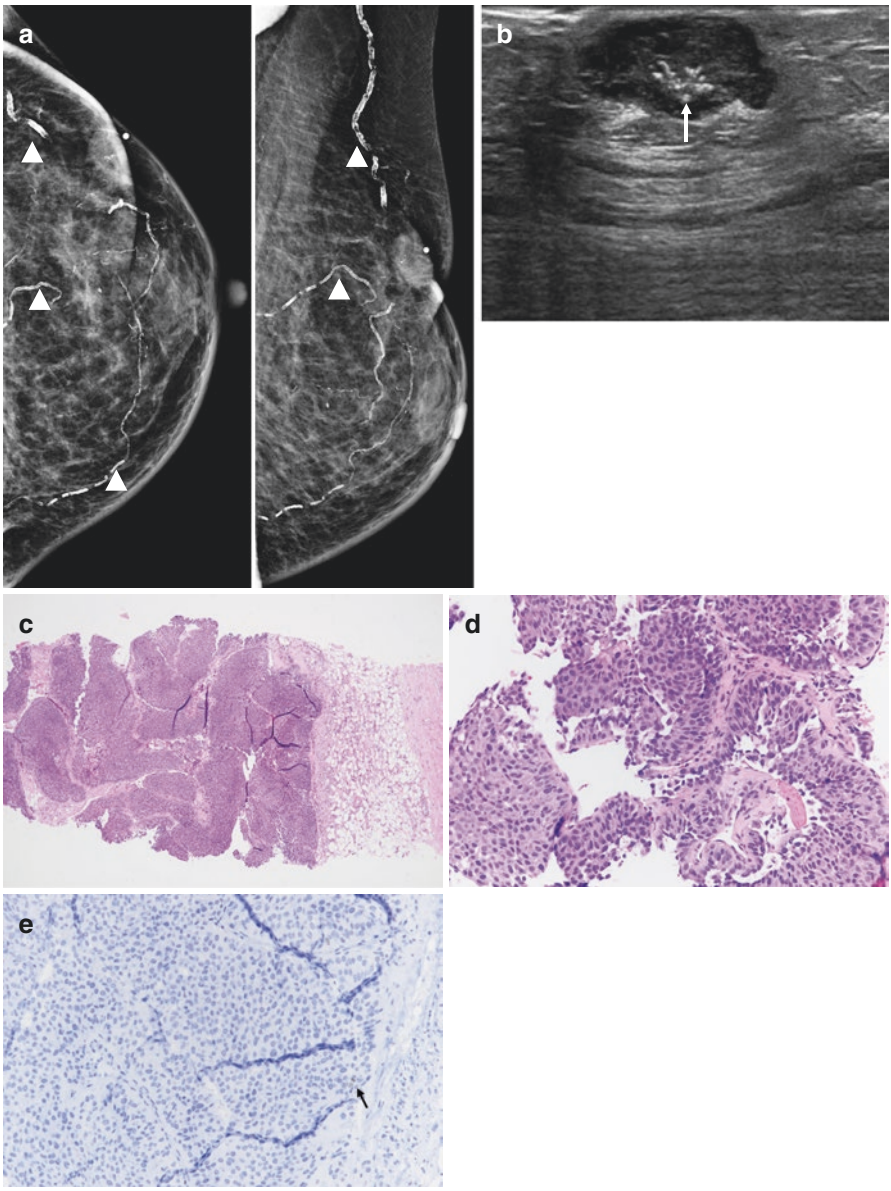
Invasive ductal carcinoma, high nuclear grade (micropapillary type). (**a**) Spot compression view of a screening detected irregular mass with partially circumscribed and spiculated margins, in a 51-year-old woman. The mass is just anterior to the pectoralis major. (**b**) Similar features are seen on ultrasound. (**c**) Needle core biopsy shows invasive ductal carcinoma with micropapillary architecture: with morular-like or nest of cells without fibrovascular core, surrounded by empty stromal spaces. The empty stromal spaces are likely fixation artifact and not lymphatic spaces. (**d**) Same micropapillary features are seen in the surgical excision specimen. (**e**) This variant of invasive carcinoma is often associated with lymph node metastasis

Case 10



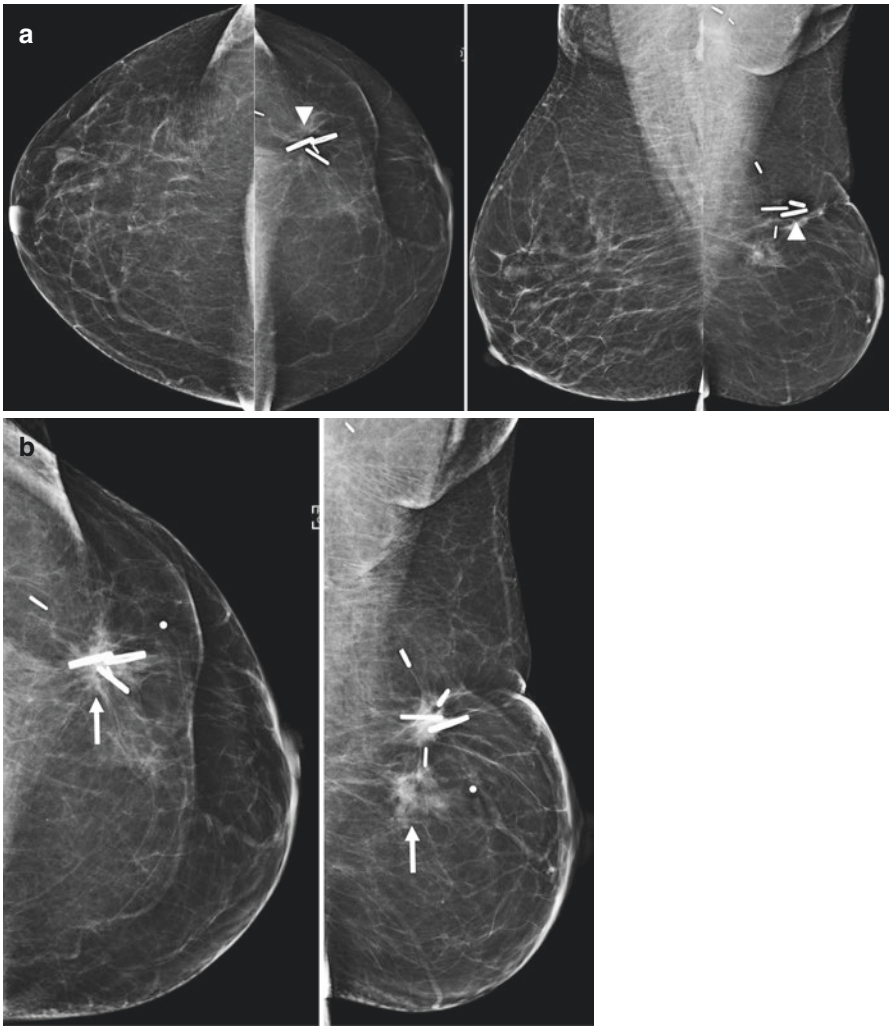
Diffuse, locally advanced invasive ductal carcinoma. (**a**) Diagnostic mammogram in a 64-year-old woman shows the right breast is shrunken, retracted, and edematous with skin and trabecular thickening. There is also global parenchymal asymmetry, on which malignant-type calcifications are superimposed. A second primary is seen as a low-density mass in the upper outer quadrant posteriorly (*arrow*). Axillary adenopathy is partially imaged (*arrowhead*), but evaluated sonographically and subsequently biopsy proven to be metastatic (not shown). (**b** and **c**) Invasive ductal carcinoma with pleomorphic nuclei with coarse chromatin and mitoses (*arrow*)

Case 11

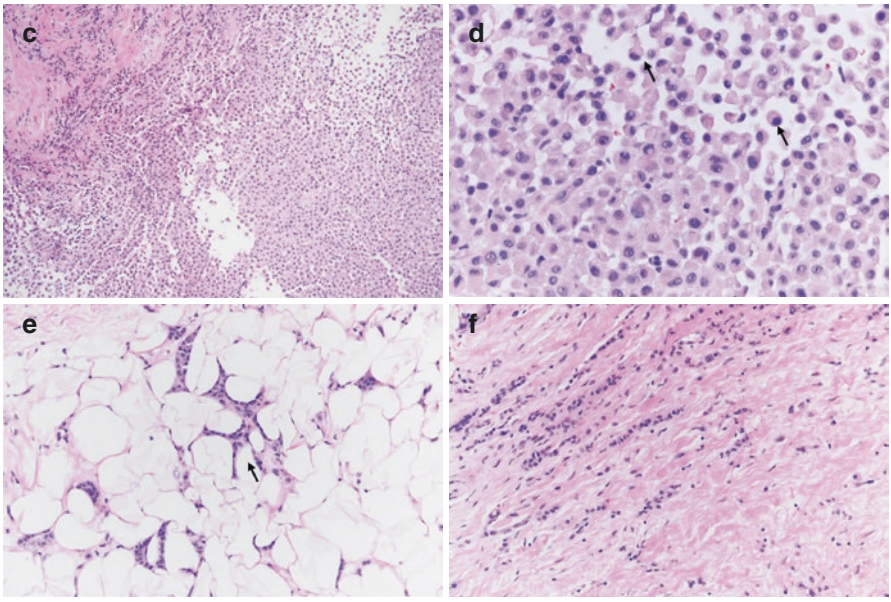


Papillary carcinoma. (**a**) A 77-year-old woman with a palpable mass containing calcifications at prior lumpectomy site, marked on skin with metallic BB. Overlying skin retraction is from surgical scarring. Vascular calcifications incidentally noted (*arrowheads*). (**b**) Lobulated complex solid and cystic mass seen on ultrasound; echogenic foci are calcifications (*arrow*). (**c**–**e**) Needle core biopsies show carcinoma with solid areas arranged around thin fibrovascular cores and collagenized stroma. The circumscribed border is characteristic of solid intraductal papillary carcinoma. Tissue fragmentation is sometimes noted. The p63 stain highlights rare myoepithelial cells at the periphery (*arrow*)

Case 12



Invasive lobular carcinoma. (**a**) Screening mammogram in a 56-year-old woman. Prior lumpectomy changes in the left breast include smaller size, skin retraction, and architectural distortion amid and inferior to vascular clips (*arrowheads*). (**b**) Palpable developing asymmetry (increasing density amidst the clips) at and inferior to lumpectomy site 1 year later. (**c** and **d**) Core-needle biopsies show solid sheet of discohesive cells, some of which are plasmacytoid (*arrows*). (**e**) Invasive lobular carcinoma may infiltrate as small nests in the breast adipose tissue. (**f**) Tumor cells are usually discohesive and low nuclear grade with single file infiltrative pattern in stromal fibrous tissue (and no desmoplasia), characteristic to lobular carcinoma. The tumor often has a concentric pattern around normal duct (not shown)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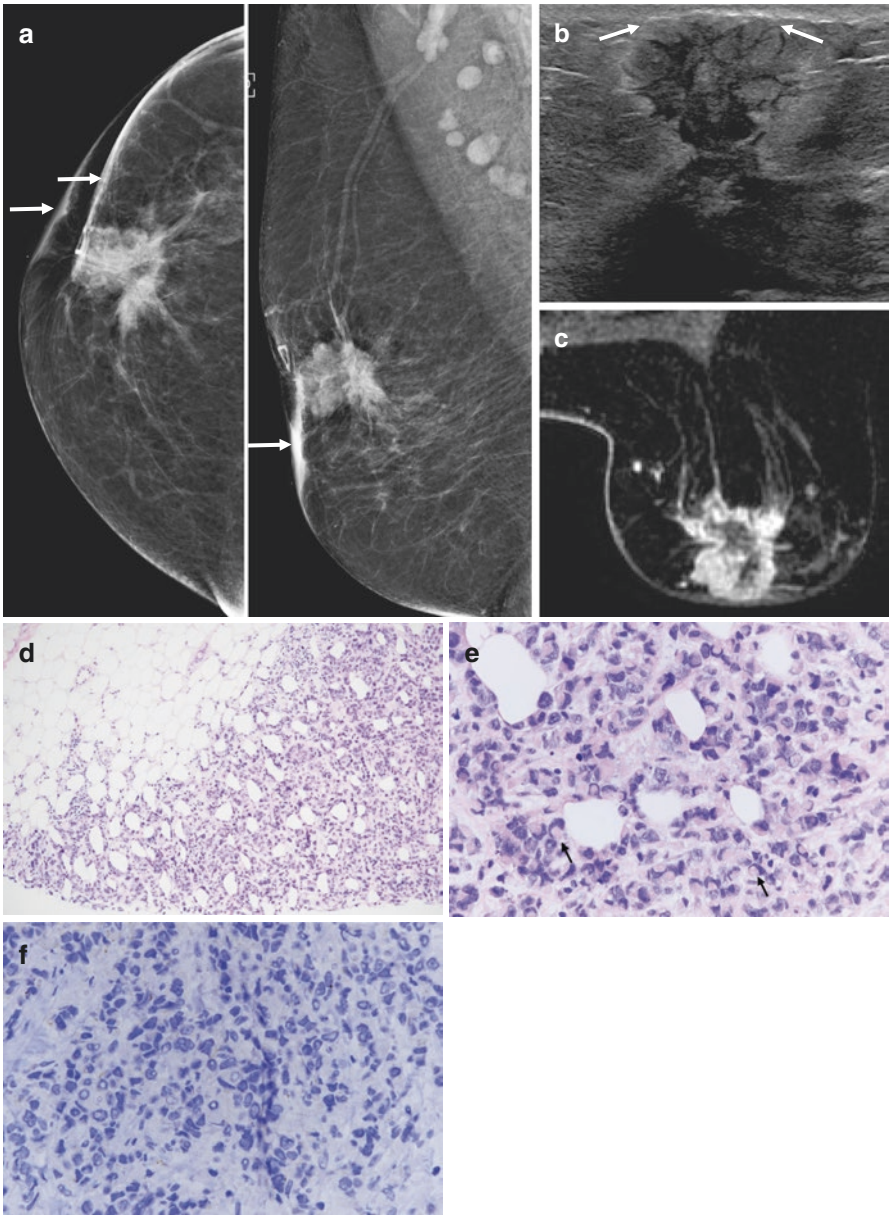
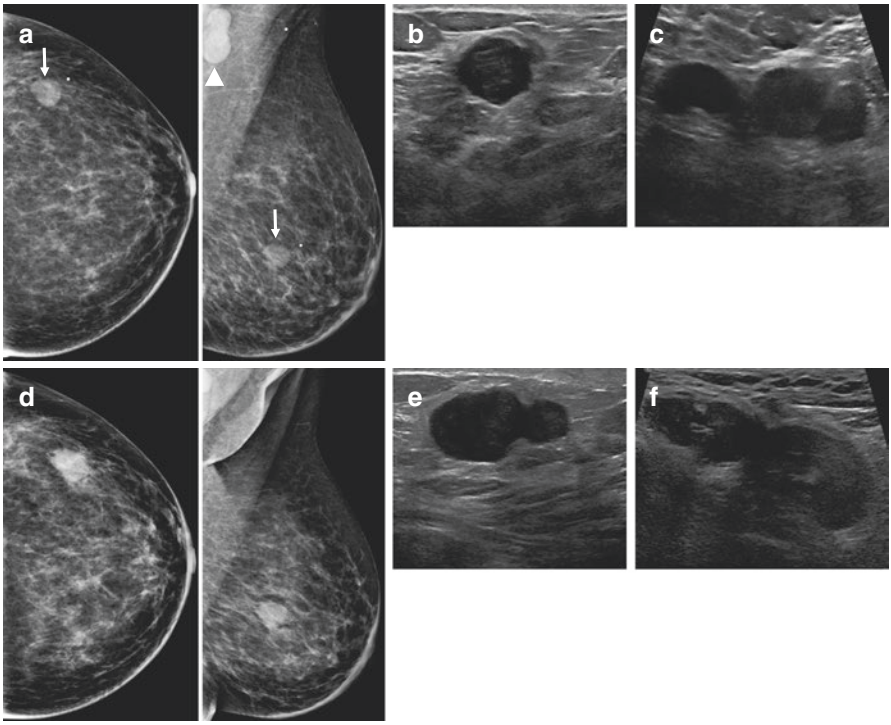
Case 13

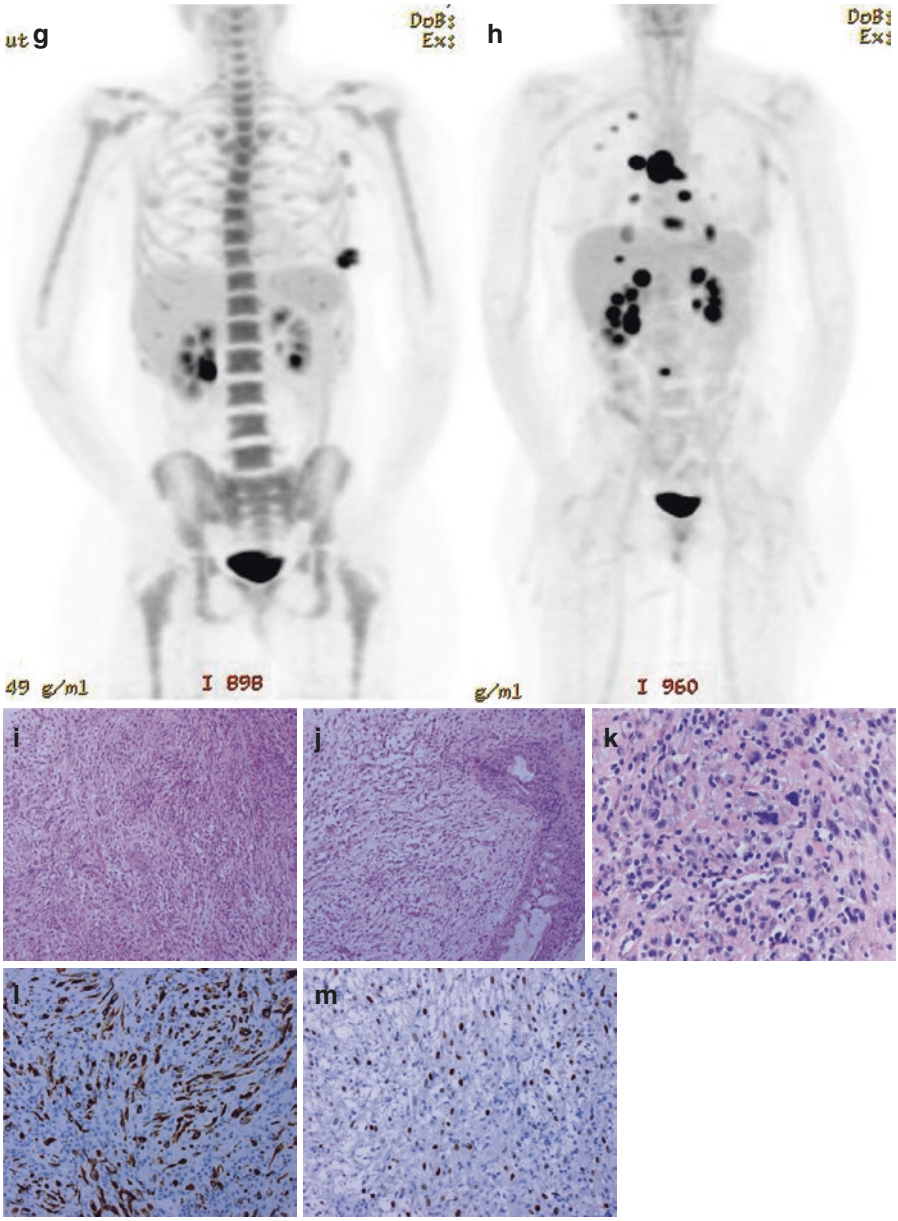


Invasive lobular carcinoma, pleomorphic type. (**a**) Diagnostic mammogram in a 65-year-old woman with a "lump." There is skin thickening and retraction overlying the mass (*arrows*). (**b**) Skin involvement is confirmed on ultrasound, as this heterogeneous mass is inseparable from the deep dermal layer (*arrows*). (**c**) Post-contrast axial MRI image showing an irregular mass with thick rim enhancement extending to the skin. (**d** and **e**) Core-needle biopsies show high nuclear grade invasive carcinoma with eccentrically placed nuclei (*arrow*), infiltrative patterns and apparent discohesion, suggestive of pleomorphic lobular carcinoma and confirmatory negative stain for e-cadherin (**f**)

Case 14



Metaplastic carcinoma with axillary metastases. (**a**) A 50-year-old woman with a palpable mass in the outer central aspect of the left breast (*arrows*) and axillary adenopathy (*arrowhead*). (**b**) Ultrasound shows solid round breast mass and (**c**) axillary adenopathy (enlarged lymph nodes with thickened cortices and no identifiable fatty hila). (**d–f**) Progression of breast mass and axillary metastases after 5 months on chemotherapy. (**g**) PET/CT 7 months into treatment and (**h**) after mastectomy, 11 months into treatment, shows continued progression. (**i**) Core needle biopsies showing atypical spindle cell proliferation. (**j**) The atypical spindle cells are adjacent to or surround non-neoplastic breast epithelium. (**k**) Pleomorphism of the atypical spindle cells is noted in some areas at higher power. (**l** and **m**) The atypical spindle cells are positive for pancytokeratin (**l**) and p63 (**m**)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Invasive Breast Cancer: Diagnosis and Management Considerations

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women [1]. Although the majority are initially identified by radiologic imaging, however, some suggest that a clinically suspicious mass detected by a patient or physician should also be biopsied, regardless of imaging findings, as about 15 percent of such lesions can be mammographically occult [2]. Breast cancer is a heterogeneous disease which comprises of many biologically different entities with distinct pathological features and clinical implications. These in turn exhibit different behaviors necessitating a tailored approach to their treatment strategies.

Breast Cancer Subtypes and Their Diagnostic Evaluation

All patients diagnosed with breast cancer should be assigned a clinical stage based on its involvement of the breast and/or nodal regions. Staging allows for efficient identification of local and systemic therapy options and provides baseline prognostic information. Pathologists who confirm the diagnosis of invasive cancer should obtain additional biomarkers for estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) in accordance with protocols laid down by the College of American Pathologists (CAP). An essential component of breast cancer treatment is complete knowledge of extent of disease and its biological features. These factors assist in estimation of risk of cancer recurrence after local therapies and provide information that predicts response to systemic therapy. Multidisciplinary coordination among breast and reconstructive surgeons, radiation and medical oncologists, radiologists, and pathologists facilitates treatment planning and streamlines patient care [3].

An important aspect of initial evaluation of women diagnosed with locally advanced breast cancer or those with persistent symptoms affecting a particular organ system includes assessment of metastatic disease with additional imaging such as CT scan, bone scan, or PET scan. Women with child-bearing potential must be offered fertility counselling. Patients diagnosed with breast cancers that are less than 40 years of age or those who have significant family history suggestive of hereditary syndromes should undergo genetic counselling and testing that may impact their surgical decision.

Classical biomarkers such as ER, PR, and HER2 together with traditional clinicopathological variables including tumor size, tumor grade, and nodal status are conventionally used to determine patient prognosis and management approach. The advent of platforms for gene expression analysis such as microarrays and RT-PCR have shown that response to treatment is not determined merely by anatomical prognostic factors but also by the molecular characteristics of individual tumors [4].

These molecular subtypes of breast cancer are also called intrinsic subtypes. The ER-positive intrinsic subtypes are called luminal tumors since the expression profiles are reminiscent of the luminal epithelial component of the breast. At least two subtypes exist within luminal-like tumors—luminal A and luminal B. Luminal A tumors have higher expression of ER-related genes and lower expression of proliferative genes than luminal B cancers. Luminal B tumors may have HER2 expression. Another intrinsic subtype called HER2-enriched tumors is characterized by overexpression of HER2. A more aggressive subtype called basal-like tumors has expression profiles that mimic that of the basal epithelial cells in normal breast tissue. This subtype is highly proliferative and is characterized by absence of expression of both hormone receptors and HER2 [5]. Despite the growing number of clinically relevant molecular subtypes being identified, current breast cancer management still depends on traditional pathology assessment supplemented with biomarker testing (tumor biology) using validated commercial assays (i.e., Oncotype Dx, MammaPrint, etc.).

Local Therapy for Breast Cancer

Primary therapy for breast cancer should provide optimal local and systemic control of disease and highest cure rate possible as measured by disease-free survival (DFS) and overall survival (OS) rates, while preserving the best possible quality of life. The treatment of breast cancer includes treatment of local disease with surgery, radiation therapy or both, and systemic treatment with chemotherapy, endocrine therapy, biologic agents, or combination of these.

Patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy based on tumor-breast ratio, patient preference, and genetic factors) with or without radiation therapy. Studies have shown that total mastectomy is equivalent to breast-conserving surgery (lumpectomy coupled with whole breast radiation) in terms of survival for the majority of women with stage I and II breast cancers [6]. Women undergoing mastectomy should be offered consultation with plastic surgeons to discuss reconstructive options. Performance of sentinel lymph node mapping and resection in surgical staging of clinically negative axillae is recommended for pathological assessment of axillary nodes in patients with early-stage cancer. Patients with clinically palpable axillary nodes with pathological confirmation of metastases should undergo axillary dissection. Following local therapy, adjuvant systemic therapy may be offered based on patient's tumor characteristics.

Whole breast radiation after breast-conserving surgery helps reduce local recurrence and has been shown to have a beneficial effect on breast cancer-related mortality. CT scan-based treatment planning helps limit radiation exposure to heart and lungs and assures adequate coverage of the lumpectomy site. Chest wall radiation after mastectomy is recommended for patients with tumors larger than 5 cm or pathologically involved margins. Nodal irradiation is considered for patients with macroscopically involved nodes. Addition of radiation to internal mammary nodes

and upper axillary nodes including the supraclavicular region has led to reduction in regional and distant recurrence as well as improvement in disease-free survival (radiation therapy to the axilla is avoided in patients who have undergone completion axillary dissection). Accelerated partial breast irradiation (APBI) refers to the use of limited, focused radiation therapy as a more convenient alternative to conventional whole breast radiation for women following breast-conserving surgery. APBI delivers a higher dose of radiation therapy per day to a limited volume of tissue encompassing the lumpectomy bed over a shorter period of time and leading to potentially less late skin toxicity. APBI is used for a highly selected group of patients and is still considered investigational while awaiting results of randomized prospective clinical trials. If adjuvant chemotherapy is indicated, then whole breast radiation is given after chemotherapy is completed; APBI may be delivered before chemotherapy or even intraoperatively.

Neoadjuvant Therapy

In certain clinical scenarios, preoperative (also known as neoadjuvant) systemic therapy is preferred. Randomized trials demonstrate similar long-term outcomes when patients are given the same systemic therapy preoperatively compared to postoperatively [7]. Preoperative systemic therapy can render surgically inoperable tumors operable and improve rates of breast conservation therapy in patients with operable breast cancer. It also allows time to make surgical decisions, particularly when waiting for genetic testing or evaluating options for reconstruction. Preoperative therapy can treat axillary nodal disease and potentially can help avoid axillary dissection in event of a good response resulting in negative sentinel nodes. Neoadjuvant therapy also allows for consideration of additional adjuvant therapy in patients with poor response to initial therapy. Certain subtypes of breast cancer such as HER2-positive and triple-negative disease are considered aggressive and likely to need adjuvant therapy. Preoperative chemotherapy is often elected for these subtypes, as it offers an opportunity to observe clinical and pathological response to systemic therapy which can provide prognostic information. Pathological complete response (pCR) to preoperative therapy is associated with an extremely favorable DFS and OS. The correlation between pCR and long-term outcome is strongest for triple negative breast cancer, followed by HER2-positive cancer and least for ER-positive disease (particularly for luminal A type tumors) [8]. Patients who are ideal candidates for preoperative systemic therapy include those with inoperable cancer, inflammatory breast cancer, bulky or matted lymph nodes, T4 or N3 disease, or patients with high tumor to breast ratio who desire breast conservation.

A number of chemotherapy regimens have activity in the preoperative setting. For most patients with hormone receptor-positive disease, particularly premenopausal patients, we recommend chemotherapy in the neoadjuvant setting rather than endocrine therapy since it is associated with higher response rates in a shorter time period. Preoperative endocrine therapy alone may be considered

for selected patients with ER-positive disease based on age, comorbidities, and low-risk luminal biology. In patients with HER2-negative cancers, anthracycline and taxane-based chemotherapy is preferred for hormone receptor positive, node-positive cancers, and triple negative cancers. For those patients in whom the potential cardiotoxic effects of anthracyclines are a primary concern, non-anthracycline regimens are a reasonable alternative. For patients with triple negative cancers, there is some early phase data to incorporate platinum agents, particularly carboplatin, in neoadjuvant therapy since it has improved pathological complete response but comes at the cost of added hematological toxicity and uncertain impact on long-term outcomes [9, 10]. National guidelines do not recommend routine addition of carboplatin to anthracycline and taxane-based chemotherapy, but it may be considered in patients with suboptimal clinical response in triple-negative disease only. Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (remainder trastuzumab is completed after surgery for a total of 1 year) [11]. Pertuzumab is added preoperatively for dual HER2 blockade for patients with greater than or equal to T2 lesions and/or N1 disease [12, 13].

Tumor response during neoadjuvant chemotherapy should be assessed routinely with clinical exam to ensure response to therapy. If there is clinical concern for lack of response or progression, then imaging such as breast ultrasound should be considered to confirm clinical exam findings. For patients experiencing progression of disease on neoadjuvant chemotherapy, alternate systemic therapy can be considered or they should be taken for surgery. All patients should undergo surgery following neoadjuvant systemic therapy, even if they have had a complete clinical and/or radiological response. However, trials are in progress to determine whether surgery can be safely omitted in highly selected patients with complete responses and negative biopsies after chemotherapy. The choice between breast conservation and mastectomy after neoadjuvant treatment is dependent on the treatment response (assessed clinically and by posttreatment imaging) and patient's tumor to breast ratio. However, patients who present with a T4 lesions or inflammatory breast cancer should undergo mastectomy following neoadjuvant treatment irrespective of their response due to higher risk for recurrence with breast conservation surgery. Patients with hormone receptor-positive breast cancer should receive adjuvant endocrine therapy to reduce the risk of breast cancer recurrence and breast cancer-related mortality. Additional postoperative chemotherapy following neoadjuvant chemotherapy and surgery is generally not indicated unless the planned course of neoadjuvant therapy could not be completed prior to surgery. There are ongoing trials exploring the role of additional chemotherapy for patients who did not achieve adequate response to neoadjuvant chemotherapy. Some examples of agents that are being studied in this setting include TDM-1 (Ado-trastuzumab emtansine) for HER2-positive patients, capecitabine or carboplatin for triple-negative cancers, and palbociclib for hormone receptor-positive cancers with residual disease after neoadjuvant chemotherapy [14–16].

Adjuvant Chemotherapy

The use of adjuvant systemic therapy is responsible for much of the reduction in cause-specific mortality from breast cancer [17]. Adjuvant chemotherapy refers to the use of cytotoxic chemotherapy after breast cancer surgery, administered with the goal of eradicating microscopic foci of cancer cells that, if left untreated, could grow and recur as metastatic cancer. The data to support adjuvant chemotherapy (versus no treatment) and, specifically, the administration of anthracycline and taxane therapy in the adjuvant setting come from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Based on EBCTCG meta-analysis, the use of an anthracycline-containing regimen compared with no treatment resulted in decreased risk of recurrence, breast cancer-specific mortality, and overall mortality [18].

The decision to use adjuvant chemotherapy takes into account tumor histology; expression of ER, PR, and HER2; tumor stage and grade; proliferation index; patient age; as well as high-risk features such as lympho-vascular invasion. Adjuvant chemotherapy is standard for patients with triple-negative breast cancer and either a tumor size greater than 0.5 cm or pathologically involved lymph nodes (regardless of tumor size). Patients with tumors that do not express hormone receptors are not candidates for endocrine therapy, and as the tumor is HER2 negative, they are not candidates for anti-HER2 therapy either. Therefore, our threshold for the use of chemotherapy in these patients is low because this is the only form of adjuvant treatment available to them. The prognosis of small (<0.5 cm), node-negative, triple-negative tumors is generally favorable. For that reason, the benefits of adjuvant chemotherapy are very small and must be weighed against the chances of serious side effects of chemotherapy.

Chemotherapy treatment decision-making for women with ER-/PR-positive, HER2-negative breast cancers is more complex, owing to the variation in prognosis among these tumors, the effectiveness of adjuvant endocrine therapy at reducing recurrence, and the variable sensitivity of ER-positive tumors to chemotherapy treatments. For such patients, the decision to administer chemotherapy is based on an assessment of the composite risk of recurrence and likelihood of benefit (traditional risk factors are taken into account such as patient age and comorbidities, tumor size and grade, lympho-vascular invasion, and lymph node status in addition to the results of gene expression profiles) [19]. Most instances of ER-positive breast cancer less than 1 cm, and all cancers less than 0.5 cm, have a good prognosis with endocrine therapy alone and do not typically require adjuvant chemotherapy. At the other end of the spectrum, most women with stage III breast cancers will warrant adjuvant chemotherapy because of their high risk of recurrence and the likely benefits of chemotherapy.

The use of microarray technology to characterize breast cancer has allowed for development of classifications systems of breast cancer by gene expression profile as mentioned earlier. There are many gene-based assays to predict prognosis such as distant recurrence or survival. The 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue is amongst the best validated prognostic assays and is most commonly

used at our institute. The 21-gene assay recurrence score (RS), also known as Oncotype Dx, has been validated both as a prognostic and a predictive tool. It helps identify those patients with *node-negative*, hormone receptor-positive breast cancer whose prognosis is so favorable that the benefit of chemotherapy is likely to be very low. The optimal RS cutoff for omission of chemotherapy remains unclear since different studies have used different cutoffs [20, 21]. Since the prospective-retrospective studies have validated RS less than 18 as a cutoff to distinguish low from intermediate RS, it is reasonable to avoid adjuvant chemotherapy for patients with node-negative, ER-positive breast cancer and an RS of less than 18. We await outcomes in women with intermediate RS from the TAILORx trial to further clarify the optimal cutoff for adjuvant chemotherapy [22]. An unplanned, retrospective subset analysis from a single, randomized clinical trial in postmenopausal, *node-positive*, ER-positive breast cancer found that RS may provide predictive information for chemotherapy benefit in this population [23]. The SWOG RxPONDER trial, which utilizes RS to assign hormone receptor-positive, HER2-negative, node-positive patients to standard endocrine therapy with or without adjuvant chemotherapy, is ongoing and will clarify the role of RS in node-positive disease.

Another commonly used assay is the 70-gene signature assay which uses microarray technology to analyze gene expression profile from breast tumor tissue to help identify patients with early-stage breast cancer likely to develop distant metastasis [24]. Results from an international randomized trial, the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial, suggest that this profile may identify subsets of patients who have a low likelihood of distant recurrence despite high-risk clinical features. However, it should be noted that the MINDACT study was not powered to exclude a benefit of chemotherapy. This assay has been approved by FDA to assist in assignment of patients with ER-positive or ER-negative breast cancer into a high or low risk for recurrence, but not for predicting benefit from adjuvant systemic therapy [25].

In general, similar chemotherapy regimens are used as adjuvant therapy in patients with ER-/PR-positive, HER2-negative cancer or with triple negative cancers. The regimen of doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) delivered on a dose-dense schedule is the preferred regimen for most patients. For patients with lower-risk disease or a history of cardiac disease, non-anthracycline regimens may be preferable; most commonly employed regimen in this setting is docetaxel and cyclophosphamide (TC). For patients in whom steroid treatment or risk of peripheral neuropathy (both are issues associated with use of taxane therapy) is a particular concern, and where there are concerns about anthracycline exposure due to cardiotoxicity, commonly recommended regimen at our institute is combination of cyclophosphamide, methotrexate, and fluorouracil (CMF). Recently published joint analysis of three adjuvant trials consisting of dose-dense doxorubicin, cyclophosphamide, and paclitaxel compared with docetaxel and cyclophosphamide showed invasive disease-free survival in favor of anthracycline-based therapy [26]. Exploratory analyses for treatment interaction by hormonal status and nodal status suggest that the benefits appear to be clinically meaningful in patients with hormone receptor negative tumors or those with hormone receptor positive tumors and positive axillary nodes.

Treatment directed against the human epidermal growth factor receptor 2 (HER2) is incorporated in the chemotherapy regimen for patients with HER2 overexpression. Initial regimen is then followed by maintenance trastuzumab to complete total therapy for 1 year based on a trial comparing no maintenance versus 1 or 2 years of trastuzumab therapy which favored 1 year of therapy; no additional benefit was derived upon continuation for 2 years [27]. The benefits of adding trastuzumab to adjuvant chemotherapy in patients with HER2-positive tumors were confirmed in a meta-analysis of eight trials of chemotherapy plus trastuzumab versus chemotherapy alone involving nearly 12,000 patients which showed significant improvement in disease-free survival and overall survival [28]. Trastuzumab is associated with cardiotoxicity which necessitates monitoring of cardiac function periodically through treatment. When trastuzumab is combined with an anthracycline-based regimen, there is an expected increase in cardiotoxicity due to overlapping side effects from trastuzumab and anthracyclines. When compared to a non-anthracycline-based chemotherapy regimen, there were more breast cancer recurrences but fewer cardiac events in the non-anthracycline arm [29]. The choice of chemotherapy backbone takes into account patient's age, cardiac risk factors, tumor characteristics, and personal preference. Trastuzumab combined with paclitaxel alone has demonstrated excellent outcomes for patients with node-negative, HER2-positive tumors that are less than 2 cm [30]. HER2-positive tumors that are smaller than 5 mm are less likely to derive benefit from adjuvant therapy including HER2-targeted therapy. There is no data to use pertuzumab in the adjuvant setting at this time, but clinical trial results evaluating this agent along with trastuzumab for 1 year are awaited.

Adjuvant Endocrine Therapy

Patients with ER-/PR-positive invasive cancer should be considered for adjuvant endocrine therapy regardless of their age, tumor type or size, lymph node status, or receipt of adjuvant chemotherapy. In patients receiving both chemotherapy and endocrine therapy, chemotherapy should be given first followed by endocrine therapy. The choice of endocrine therapy is dependent on menopausal status of the patient prior to administration of chemotherapy. Tamoxifen is a commonly used selective estrogen receptor modulator in premenopausal women. In the Suppression of Ovarian Function (SOFT) trial, premenopausal women were randomly assigned to one of three arms: tamoxifen alone, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression. Ovarian suppression was achieved with the use of the gonadotropin-releasing-hormone agonist triptorelin, oophorectomy, or ovarian irradiation. Compared to tamoxifen alone, tamoxifen plus ovarian suppression did not result in improved outcomes but caused increased toxicity which likely resulted in a higher rate of medication discontinuation. In a subgroup analysis, women at high risk of recurrence, who received prior chemotherapy, had improved outcomes with addition of ovarian suppression [31]. Tamoxifen and Exemestane Trial (TEXT) evaluated comparison between tamoxifen plus ovarian suppression and exemestane plus ovarian suppression. When these two adjuvant endocrine therapy trials (SOFT and TEXT) were combined to compare tamoxifen plus ovarian suppression and exemestane plus ovarian

suppression, the latter showed improved rate of freedom from breast cancer at 5 years [32]. Based on the combined results of SOFT and TEXT trials, exemestane plus ovarian suppression is preferred for premenopausal, hormone receptor-positive breast cancer at higher risk of recurrence (patients who are less than 35 years and those that received chemotherapy). Optimal duration of tamoxifen was evaluated by comparing 5 years of tamoxifen to 10 years. Tamoxifen therapy extended to 10 years reduced risk for recurrence and breast cancer-specific mortality at the cost of increased incidence of pulmonary embolism and endometrial cancer [33].

Aromatase inhibitors have consistently been shown to improve outcomes for postmenopausal women with hormone receptor-positive breast cancer compared with tamoxifen. All the available aromatase inhibitor agents (anastrozole, letrozole, and exemestane) have demonstrated similar efficacy and toxicity profiles. Aromatase inhibitors can be utilized as initial adjuvant therapy, or as sequential therapy following 2–3 years of tamoxifen or as extended therapy beyond 5 years of tamoxifen. Sequential therapy of aromatase inhibitor after tamoxifen has been shown to improve overall survival. The extension of treatment with an adjuvant aromatase inhibitor to 10 years resulted in significantly higher rates of disease-free survival and a lower incidence of contralateral breast cancer than those with placebo, but the rate of overall survival was not higher with the aromatase inhibitor than with placebo [34]. Aromatase inhibitors can be associated with hot flashes, musculoskeletal symptoms such as stiffness and joint pain, as well as long-term effects such as osteoporosis and increased cardiovascular risk.

Post-therapy Surveillance

Follow-up care is provided by the members of the treatment team. All women should have a careful history every 3–6 months for the first 3 years after primary therapy, then every 6–12 months for the next 2 years, and then annually. It is recommended that all women should perform monthly breast self-examination. Mammography should be performed annually with first posttreatment mammogram 6 months after completion of radiotherapy [35]. For women who have undergone mastectomy, surveillance is usually performed by physical examination. Because the majority of recurrences occur between scheduled visits, it is prudent to inform women about symptoms of recurrence. Patients on adjuvant tamoxifen with intact uterus should undergo yearly gynecologic assessment and rapid evaluation of abnormal vaginal bleeding due to risk of endometrial cancer associated with tamoxifen use. Patients on aromatase inhibitor (AI) therapy should undergo monitoring of bone health at baseline and periodically thereafter. Bone strengthening agents can be employed for patients on AI therapy who have suboptimal bone health. The data are insufficient to suggest routine laboratory assessments including tumor markers and surveillance imaging in absence of symptoms [35]. Adequate symptom management for women on endocrine therapy improves medication adherence. Reproductive issues may arise during endocrine therapy including sexual dysfunction, fertility, and contraception which need coordination of care with gynecology. Lifestyle modification can be an empowering and effective way to boost physical

and mental health in breast cancer survivors and possibly to improve outcomes. Observational data suggest that physical activity to optimize body-mass index and minimization of alcohol intake are associated with a decreased risk of breast cancer recurrence and death in breast cancer survivors [36, 37].

Recurrent or Metastatic Breast Cancer

Recurrent breast cancer can present as local recurrence or distant metastasis. Local recurrence usually presents as a palpable lump in the breast, chest wall, or nodal region, or as new findings on mammography. All patients with local recurrence should undergo biopsy for pathological confirmation and imaging to assess for concurrent distant metastatic disease. In the absence of distant metastases, patients must undergo surgical resection of the recurrence along with nodal sampling followed by involved field radiation therapy if not previously treated or if additional radiation can be administered safely. Based on the CALOR trial, after local treatment, women with local recurrences should be considered for systemic therapy with chemotherapy and/or endocrine therapy if applicable, for a limited duration with similar intent as that of adjuvant therapy. The choice of chemotherapy depends on the biomarkers, previous therapy, and time to recurrent disease [38].

Metastatic breast cancer involving distant sites cannot be cured, but significant improvements in breast cancer-specific survival have been observed with the use of systemic therapies, with some patients achieving long-term remissions [39]. Current practice guidelines recommend that patients with metastatic disease must be biopsied to confirm tumor histology and allow reevaluation of biomarkers. Assessment of ER, PR, and HER2 should be repeated as there may be discordance between the primary and metastatic cancers. This discordance could be related to change in the biology of the tumor, differential effect of prior treatment resulting in clonal selection, or tumor heterogeneity [40, 41]. The treatment strategy is a tailored approach and depends upon tumor biology and biomarkers as well as clinical factors pertaining to the patient such as volume and location of metastatic disease and patient's functional and nutritional status. Although a subset of patients with oligo-metastatic disease may benefit from an intensified locoregional approach, most patients with metastatic breast cancer receive systemic medical therapy consisting of chemotherapy, endocrine therapy, and/or biologic therapies and supportive care measures [42]. The primary goals of systemic treatment for metastatic breast cancer are prolongation of survival, palliation of symptoms, and maintenance or improvement in quality of life.

Women with hormone receptor-positive and HER2-negative metastatic disease should generally be considered for initial endocrine therapy. However, sometimes patients may present with rapidly progressive, symptomatic disease with end-organ dysfunction (visceral crisis which could involve lungs, liver, or compression of important structures), in which case chemotherapy can be chosen over endocrine therapy. Endocrine therapy choices depend on prior exposure to antiestrogen agents. There is some data in postmenopausal women to suggest that aromatase inhibitor therapy appears to have superior outcomes compared to tamoxifen [43, 44]. Fulvestrant (ER down-regulator)

when compared to anastrozole as first-line agent in metastatic ER-positive breast cancer who had not received prior hormone therapy showed improved progression-free survival [45]. Compared with anastrozole alone, combination of fulvestrant and anastrozole resulted in an improvement in progression-free and overall survival. On subgroup analysis, the benefit of combination therapy appeared to be limited to endocrine therapy naïve patients [46]. Observation of synergy between CDK 4/6 inhibitors and endocrine therapy has led to emergence of newer combinations for therapy in this population. Palbociclib (CDK 4/6 inhibitor) in combination with letrozole (AI) when compared to letrozole alone showed improved response rates and progression-free survival [47]. Ribociclib, another selective CDK 4/6 inhibitor, in combination with letrozole demonstrated improved efficacy over letrozole alone [48]. CDK 4/6 inhibitors are generally well tolerated, most commonly notable adverse effects include neutropenia, fatigue, derangements of liver function, and nausea. Combination of mTOR inhibitors with endocrine therapy was postulated to overcome resistance to endocrine therapy. An improvement in progression-free survival and response rates was seen with combination of everolimus (mTOR inhibitor) and exemestane (steroidal AI) in patients who had progressed on anastrozole [49]. Everolimus is associated with significant toxicity including stomatitis, pneumonitis, abnormal liver function, hyperglycemia, and fatigue.

Women with hormone receptor-negative metastatic disease or those with hormone receptor-positive disease that have either become refractory to endocrine therapy or have significant tumor burden are considered for chemotherapy. Combination chemotherapy when compared to single agents given sequentially generally provides quicker and higher rates of responses and has longer time to progression but comes at the cost of increased toxicity. There is no compelling evidence that suggests that combination chemotherapy is superior to sequential chemotherapy and the latter is generally preferred for better quality of life. However, combination therapy is preferred in patients with rapidly progressive disease with impending end-organ failure where quicker response is desired. Single-agent chemotherapy is continued until there is evidence for disease progression at which time another agent is chosen based on previous therapy, toxicity profile, logistics of administration, and patient preference. A variety of chemotherapy agents (used as single agents or in combination) are active in breast cancer including anthracyclines (doxorubicin, epirubicin, and pegylated liposomal doxorubicin), taxanes (paclitaxel, docetaxel, and albumin-bound paclitaxel), antimetabolites (capecitabine and gemcitabine), non-taxane microtubule inhibitors (eribulin and vinorelbine), platinum agents (cisplatin and carboplatin), and others such as ixabepilone, cyclophosphamide, and methotrexate. The role of immune therapy in metastatic breast cancer, particularly triple-negative disease, continues to evolve at this time. The duration of chemotherapy should be individualized taking into account the patient's goals of therapy, presence of treatment toxicities, and alternative options that might be available. In general, patients should continue chemotherapy to the best response or disease progression unless toxicity requires discontinuation of treatment sooner. A detailed discussion about the chemotherapy regimens is beyond the scope of this chapter.

For patients with HER2-positive metastatic breast cancer, HER2-directed agents should be a component of treatment. For most patients, HER2-directed agent plus chemotherapy is chosen. However, patients with hormone receptor-positive and

HER2-positive metastatic breast cancer may receive HER2-directed therapy in combination with endocrine therapy, if they have low volume, indolent, and asymptomatic disease, especially in the elderly. The preferred first-line therapy option is combination of trastuzumab, pertuzumab, and docetaxel which has shown improved response rates, progression-free survival, and overall survival when compared to trastuzumab and docetaxel [50, 51]. Common adverse effects from this therapy include febrile neutropenia, diarrhea, rash, mucositis, and edema. There was no increase in the rate of ventricular dysfunction with the combination. After achievement of best response to treatment, cytotoxic chemotherapy is typically discontinued with plan to continue trastuzumab and pertuzumab therapy until disease progression. In patients whose tumors are also hormone receptor positive, endocrine therapy is added to HER2-directed therapy following discontinuation of chemotherapy. Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate composed of trastuzumab, a thioether linker, and a microtubule inhibitor, DM1. This is typically utilized in second-line setting based on improved outcomes in terms of progression-free and overall survival and better toxicity profile when compared to lapatinib plus capecitabine [52]. This could be an alternative first-line treatment for patients unable to receive trastuzumab plus pertuzumab plus taxane, based on non-inferiority and better tolerability of TDM-1 alone or in combination with pertuzumab, when compared to trastuzumab and taxane therapy [53]. The regimen of capecitabine plus lapatinib is an option for patients with HER2-positive disease following progression on trastuzumab containing regimen based on improved time to progression with the combination compared to capecitabine alone [54]. This is reserved as a third-line option after failure of abovementioned regimens.

Distant sites of recurrence may require local therapies to alleviate symptoms and prevent impending complications. Surgery/procedures, radiation, or regional chemotherapy (intrathecal) may be employed as needed for metastatic sites such as brain metastases or leptomeningeal involvement, pleural or pericardial effusion, impending pathological fracture or compression of vital organs, biliary or urinary obstruction, bleeding, cord compression, painful bone metastases, or soft tissue disease.

Monitoring of metastatic disease during therapy is important to make sure that the therapy is providing benefit and the patient does not have toxicity from ineffective therapy. Monitoring of disease entails periodic assessment of symptoms and clinical exam (if disease is easily accessible clinically) to determine response. These are coupled with laboratory tests including serial tumor markers if elevated and periodic imaging (CT scan, bone scan, MRI as indicated) to ensure disease response to therapy. Data on circulating tumor cells suggest their prognostic value, but their use in disease monitoring is controversial and should not be used to influence treatment decisions at this time.

Summary

The therapeutic options for patients with invasive breast cancer are complex. An essential component of patient's management is the multidisciplinary team approach that includes collaboration among breast radiologist, pathologist, breast

and reconstructive surgeons, medical and radiation oncologists, palliative care specialist, fertility specialist, genetic counsellors, nurse navigators, and clinical trial coordinators. *The patients and physicians share the responsibility to explore and identify the most appropriate treatment options in order to optimize the chance of cure and minimize toxicity depending on individual patient factors and disease variables*. Participation in clinical trials helps patients access emerging novel therapies and contribute to the improvement in therapeutic outcomes.

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Suggested Readings for the Radiology Section

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