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CASE MANAGEMENT

Triple-Negative Breast Cancer

A 46-year-old black woman presents to Indiana University Health with a left breast mass detected on screening mammography. Diagnostic imaging demonstrates a 2.7 cm irregular mass and an enlarged axillary lymph node *(Figure 1* *see page 2)*. Core biopsies are obtained and confirm the presence of invasive ductal carcinoma in the breast that is estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor type 2 (Her-2/neu) negative. The lymph node is positive for tumor. Clips are left at both biopsy sites. Subsequent genotyping shows the patient is negative for the *BRCA* mutation.

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Dr. Kandice Ludwig has disclosed that her spouse is a surgeon and part owner of the Naab Road Surgery Center. Any potential conflict of interest has been resolved.

OBJECTIVES
After reading this article, the reader should be able to:

- Identify the most common type of breast cancer.
- Discuss triple-negative breast cancer (TNBC) with regard to its characteristics, incidence, risk factors, and prognosis.
- Summarize the roles of neoadjuvant chemotherapy and postoperative radiation therapy for TNBC.
- Compare and contrast techniques for the localization of nonpalpable breast lesions.
- Describe the management of relapsed TNBC.

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Overview of Invasive Ductal Carcinoma and Triple-Negative Breast Cancer

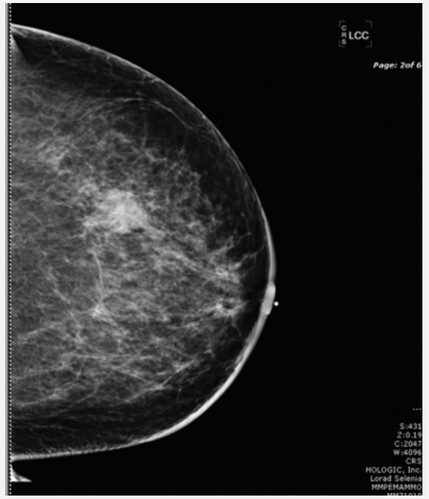
Invasive/infiltrating ductal carcinoma (IDC) is the most common type of breast cancer, accounting for approximately 80 percent of all diagnoses and more than 144,000 new US cases annually.[1] Triple-negative breast cancer (TNBC), a molecularly diverse subgroup defined by a lack of ER, PR, and Her-2/neu expression, comprises about 15 percent of all IDC cases.[2] Black race is a significant risk factor for TNBC, with a recent analysis of nearly 39,000 patients with triple-negative IDC finding that 24 percent were black, while only 12 percent were white.[2]

Other major risk factors for TNBC include younger age at presentation, Hispanic ethnicity, and germline mutations in DNA-damage repair-pathway genes, namely *BRCA1* and *BRCA2*. In excess of 80 percent of breast cancers among patients with a hereditary *BRCA1* mutation are triple-negative.[3] Moreover, even sporadic TNBC shares many clinical and molecular features with *BRCA1*-associated cancers, including defective DNA repair.

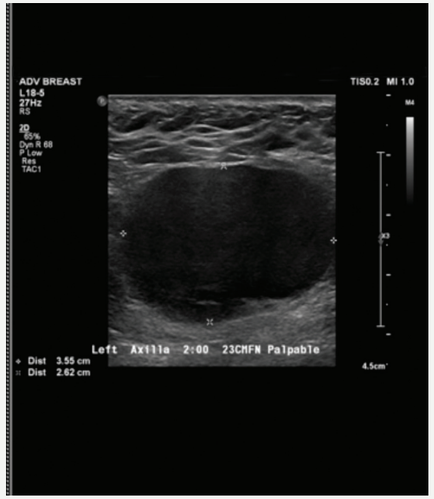
"At the time of presentation, triple-negative tumors tend to be larger and of higher histologic grade than other breast cancer subtypes," reports Kandice Ludwig, MD, assistant professor of clinical surgery at Indiana University School of Medicine and general surgeon at IU Health. "These tumors are also more aggressive, marked by shorter intervals to locoregional recurrence, increased rates of visceral and central nervous system metastases, and reduced disease-free survival rates."[2,4-6]

Unlike hormone-receptor-positive breast cancers, TNBC cannot be treated with endocrine therapy or therapies targeted to Her-2/neu (e.g., trastuzumab) and may be associated with a poor prognosis.[7] Nonetheless, some TNBCs are potentially curable.

Figure 1. Initial imaging of the breast and axilla



A. *Mass in the upper outer quadrant of the left breast on mammography. The patient had skin thickening but a negative skin biopsy.*



B. *Enlarged palpable node in the left axilla, with a loss of normal architecture and complete replacement by tumor.*

The patient is evaluated by breast surgery and medical oncology. Staging studies are performed and show substantial tumor burden in the axillary lymph nodes but no evidence of metastatic disease (Stage IIIC).

Neoadjuvant Chemotherapy

The concept of neoadjuvant therapy for early breast cancer without distant metastases has changed substantially over the last two decades and is now considered standard of care for some tumors, almost independent of their size. In addition to facilitating breast-conserving surgery by reducing local tumor burden, neoadjuvant therapy also serves as an in vivo sensitivity test for the applied treatment regimen.

Systemic chemotherapy remains the foundation of treatment for patients with TNBC, as no targeted therapeutics are currently approved for use.[8] Standard neoadjuvant regimens typically include an anthracycline (doxorubicin or epirubicin) plus an alkylating agent (cyclophosphamide), given either concurrently with a taxane (docetaxel) or sequentially before or after a taxane (docetaxel or paclitaxel).[8] Platinum-containing agents are not usually incorporated outside the clinical trial setting because of drug toxicity and lack (to date) of clear survival benefits. These drugs may be considered in selected patients with *BRCA1/2* mutations.

Approximately 13 to 22 percent of patients with TNBC are markedly sensitive to neoadjuvant chemotherapy and experience a complete pathologic response.[9]

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The patient is started on neoadjuvant chemotherapy, consisting of four cycles of doxorubicin and cyclophosphamide administered every three weeks followed by 12 cycles of weekly paclitaxel. She has an excellent clinical response to treatment, with the tumor no longer palpable on breast examination, and ultrasound imaging showing no visible breast mass and a reduction in the size of the axillary nodes. She is offered and agrees to the option of breast-conserving surgery.

Nonpalpable Breast Lesion Localization and Excision

Wire and Seed Localization

"Guidewire placement is the traditional approach for localizing nonpalpable breast lesions," Dr. Ludwig says. "This technique, developed more that 20 years ago, is generally successful but has notable disadvantages, including patient anxiety and discomfort; potential for wire displacement because of its external component; and the possibility of wire transection or breakage, leaving fragments in the breast.

"In addition, the wire entry point through the skin may be suboptimal for the surgical approach, which is often determined by the desired cosmetic outcome," continues Dr. Ludwig. "Another drawback to wire localization is that it must be performed the day of surgery, which couples radiology and surgery scheduling and may lead to operating room delays."

Radioactive seed localization using 125 iodine (I^{125}) was developed in response to many of the issues associated with wire localization. However, radiation safety precautions limit the use of this approach at some institutions and outpatient centers.

Figure 2. SAVI SCOUT radar localization system

The handpiece emits non-radioactive, electromagnetic waves to detect and confirm the locations of the reflector from the surface of the patient's breast. The console provides audible and visual feedback that increases in cadence with proximity of the reflector to the handpiece.

Radar Localization

The SAVI SCOUT® system (Cianna Medical), approved by the US Food and Drug Administration in 2014, harnesses micro-impulse radar technology to localize and remove breast lesions. Instead of wires, the radiologist places a small reflector into the breast up to 30 days before surgery. The SCOUT guide, which emits the radar signal, allows the surgeon to detect the location of the reflector. Real-time audible and visual indicators from the radar console *(Figure 2)* assist in accurately locating the reflector and target tissue.

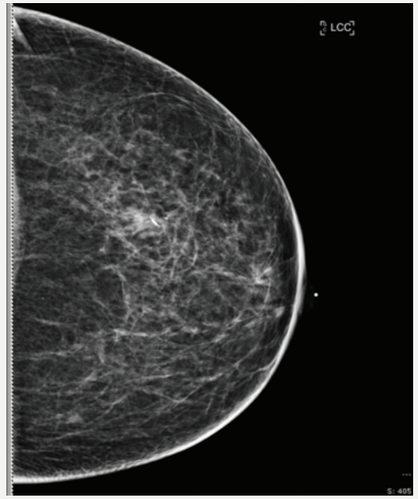
SAVI SCOUT was evaluated in a multicenter, prospective, single-arm trial that enrolled 154 patients scheduled for excisional biopsy or breast-conserving surgery for a nonpalpable breast lesion.[10] SCOUT reflectors were inserted up to seven days before surgery, with placement confirmed by mammography or ultrasonography. The reflectors were successfully placed in 153 of the patients, and all lesions and reflectors were removed during surgery. The study investigators concluded that SCOUT is a reliable and effective alternative method for the localization and surgical excision of nonpalpable breast lesions without the need for wires or radioactive materials.

"IU Health adopted the SAVI SCOUT technology in January 2017, and it quickly became the standard technique for localizing nonpalpable lesions in the breast and axilla because of its ease of use and efficacy," notes Dr. Ludwig. "Approximately 50 lesions have been localized to date, all of which were successfully removed."

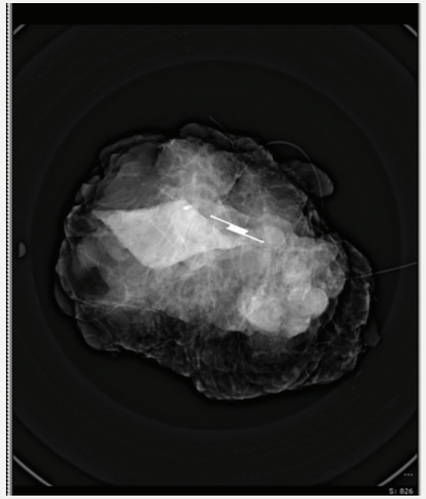
According to Dr. Ludwig, the SCOUT reflector is often placed during the preoperative teaching visit. Such timing not only enhances patient comfort but minimizes operative day waiting times and delays.

The patient undergoes lumpectomy with axillary dissection. The SAVI SCOUT is used to localize and remove the patient's breast lesion and previously biopsied axillary node *(Figure 3)*. Final pathology shows no residual tumor in the breast or 11 lymph nodes, indicative of a complete pathologic response.

Figure 3. Localization film and breast lesion documentation at lumpectomy



A. *Post-localization mammogram with biopsy clip and SCOUT placement.*



B. *Operating room specimen mammogram documenting excision of the lesion with biopsy clip and SCOUT.*

Postoperative Radiation Therapy

Patients with TNBC undergoing breast-conserving surgery receive postoperative radiation therapy to decrease the risk of locoregional recurrence and increase overall survival. A retrospective study of 468 patients with stage I to III TNBC found adjuvant radiation significantly improved survival in the 178 patients who underwent breast-conserving surgery, although it conferred no survival benefit in the simple mastectomy or modified radical mastectomy groups.[11]

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The patient receives 30 doses of radiation therapy that includes comprehensive nodal irradiation and a boost to the tumor bed. She is being monitored closely for treatment-related side effects and signs of relapse.

TNBC Relapse

The risk of relapse among patients with TNBC with residual disease at the time of surgery is 20 to 30 percent.[12] No consensus has been reached regarding the use of additional chemotherapeutic agents in this setting, and clinical trial participation may be considered *(see sidebar)*. A recently completed study that enrolled more than 900 women found that adjuvant capecitabine prolonged disease-free and overall survival in this patient population.[13]

"Considerable research is underway focusing on the identification and elucidation of 'drugable' targets and pathways that underlie the aggressive biology of this heterogeneous disease. Ongoing efforts in this area will ensure the emergence of novel strategies for the management of triple-negative breast cancer," Dr. Ludwig concludes.

A recently completed study that enrolled more than 900 women found that adjuvant capecitabine prolonged disease-free and overall survival in this patient population.

Randomized Controlled Trial of Genomically-Directed Therapy in Patients With TNBC

Patients with TNBC and significant residual invasive disease at the time of surgery who received neoadjuvant chemotherapy and, in the case of those undergoing breast-conserving surgery, postoperative radiotherapy are eligible to participate in a phase II multicenter national clinical trial (NCT02101385). The purpose of the study is to test the theory that therapy designed for an individual's specific tumor will improve outcomes compared with standard of care, which currently is observation alone.

Patients randomized to the experimental study arm will receive an FDA-approved drug at standard dose for four cycles (12 to 16 weeks total duration). Treatment will be assigned to each participant individually on the basis of biomarkers/pathways identified by DNA sequencing. Patients in the control arm will be observed, with additional treatment, including capecitabine, permitted at the discretion of the treating physician. The primary study outcome measure is two-year disease-free survival.

The Hoosier Oncology Group designed the study protocol; Bryan Schneider, MD, associate professor of medicine and medical/molecular genetics at IU School of Medicine, is the principal investigator. For more information contact:

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Dr. Ludwig received her medical degree from Louisiana State University School of Medicine in New Orleans, did a residency in general surgery at Texas A&M University Health Science Center in Temple, and completed a fellowship in breast surgical oncology at the University of Michigan in Ann Arbor. Her clinical interests focus on all aspects of breast care, including both benign breast disease and breast cancer and surveillance of/risk reduction in women at high risk for breast cancer. Among her surgical interests are nipple-sparing mastectomy, oncoplastic breast surgery, and axillary management.

A member of the American Society of Breast Surgeons and other professional organizations, Dr. Ludwig is an editorial reviewer for the *Annals of Surgery, Annals of Surgical Oncology, Clinical Breast Cancer,* and *Journal of Pediatric Surgery.* An active participant in the Alliance for Clinical Trials in Oncology and the Translational Breast Cancer Research Consortium, she serves as the local or co-principal investigator for several collaborative breast cancer clinical trials and other studies examining quality of life indicators in breast cancer survivors.

In 2015, Dr. Ludwig was named the medical director of IU Health North Breast Care, and she was awarded the IU School of Medicine Board of Trustees teaching award in 2016.

References

1. American Cancer Society. Cancer Facts & Figures 2017. Available at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html.
2. Plasilova ML, Hayse B, Killelea BK, Horowitz NR, Chagpar AB, Lannin DR. Features of triple-negative breast cancer: Analysis of 38,813 cases from the national cancer database. *Medicine (Baltimore).* 2016;95(35):e4614.
3. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *J Clin Oncol.* 2002;20(9):2310-2318.
4. Zaky SS, Lund M, May KA, et al. The negative effect of triple-negative breast cancer on outcome after breast-conserving therapy. *Ann Surg Oncol.* 2011;18(10):2858-2865.
5. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat.* 2012;133(3):831-841.
6. Billar JA, Dueck AC, Stucky CC, et al. Triple-negative breast cancers: unique clinical presentations and outcomes. *Ann Surg Oncol.* 2010;17 Suppl 3:384-390.
7. Newman LA, Reis-Filho JS, Morrow M, Carey LA, King TA. The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: triple-negative breast cancer. *Ann Surg Oncol.* 2015;22(3):874-882.
8. Andreopoulou E, Kelly CM, McDaid HM. Therapeutic Advances and New Directions for Triple-Negative Breast Cancer. *Breast Care (Basel).* 2017;12(1):21-28.
9. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384(9938):164-172.
10. Cox CE, Russell S, Prowler V, et al. A Prospective, Single Arm, Multi-site, Clinical Evaluation of a Nonradioactive Surgical Guidance Technology for the Location of Nonpalpable Breast Lesions during Excision. *Ann Surg Oncol.* 2016;23(10):3168-3174.
11. Steward LT, Gao F, Taylor MA, Margenthaler JA. Impact of radiation therapy on survival in patients with triple-negative breast cancer. *Oncol Lett.* 2014;7(2):548-552.
12. National Comprehensive Cancer Network. NCCN guidelines for the treatment of breast cancer. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
13. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med.* 2017;376(22):2147-2159.

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