Clinical Pearls

- Triple-negative breast cancers occur more commonly in younger patients and vary with race, ethnicity, and socioeconomic status.
- Patients with triple-negative breast cancer have an aggressive natural history, with the risk of distant recurrence highest during the first 3–5 years after diagnosis.
- Visceral metastases are more common in triple-negative breast cancer compared to ER-positive breast cancer, and the most frequent sites of distant disease include the lungs and central nervous system.
- The triple-negative breast cancer subtype responds well to cytotoxic chemotherapy with increased rates of pathologic complete response after neoadjuvant chemotherapy, but poorer prognosis compared with non-triple-negative breast cancer, which is a phenomenon referred to as the triple-negative paradox.

2.1 Definition of Triple-Negative Breast Cancer

TNBCs are defined by what they are not, that is, tumors that do not express any of the three prognostic and predictive biomarkers used in routine clinical management: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2). Standardization in the assessment of these biomarkers has gone through changes through the years [1]. Current testing guidelines define the lack of ER and PR receptors as ≤1% tumor staining on immunohistochemistry (IHC) [2]. The joint publication of guidelines for HER2 testing by the
American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) was updated in 2013 and provides recommendations for optimal HER2 testing [3].

TNBC has been further divided into subgroups on the basis of histopathological features and/or gene expression profiling highlighting the heterogeneity and complexity of these tumors [4–7]. From a histologic perspective, TNBC also consists of other subtypes such as secretory or adenoid cystic tumors which are relatively less aggressive and metaplastic breast cancers which are high-grade and aggressive tumors. Four distinct intrinsic subtypes (luminal A, luminal B, HER2 enriched, and basal-like) of prognostic and predictive significance, identified using DNA microarray analysis, were first described by Perou and colleagues in 2000 [8]. Of the four, the basal-like tumors typically are of the triple-negative phenotype, and a vast majority (~80%) of TNBCs are of the basal-like subtype [6, 9]. Another classification of TNBC subtypes through gene expression profiling identifies six distinct molecular subtypes (basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stemlike, and luminal androgen receptor) [5]. This was refined into four tumor-specific subtypes (basal-like 1, basal-like 2, mesenchymal, and luminal androgen receptor) following histopathology and laser-capture microdissection which identified infiltrating lymphocytes and tumor-associated stromal cells contributing to the immunomodulatory and mesenchymal stemlike subtypes, respectively [6]. Clinical trials evaluating the various subgroups and the benefits of different treatment strategies are awaited.

2.2 Epidemiology and Risk Factors

Breast cancer is the most frequent cancer in women and the fifth leading cause of cancer death worldwide [10, 11]. Breast cancer remains common regardless of region; however, incidence rates vary globally. For example, incidence rates range from 27 per 100,000 in Middle Africa to 92 per 100,000 in Northern America [11]. About 15–20% of all invasive breast cancers are of the TNBC subtype which corresponds to approximately 170,000 cases of TNBC globally [10, 12–14].

2.2.1 Age, Ethnicity, and Race

TNBC is more common in younger patients [13, 14] and varies according to race and ethnicity. Studies have consistently reported overrepresentation of TNBC among African American women [9, 14, 15]. The Carolina Breast Cancer Study was a population-based, case-controlled study of environmental and molecular determinants of breast cancer risk [9]. Patients with basal-like tumors as defined by IHC markers (ER−, HER2−, cytokeratin 5/6+, and/or HER1+) were more likely to be African American and premenopausal [9]. The prevalence of basal-like breast cancers in African Americans was 26% as compared to 16% in non-African
American cases in the study [9]. The high prevalence was seen mostly in premenopausal African American women in whom the prevalence was 39% [9]. Similarly, a population-based study using the California Cancer Registry data identified 12.5% of the eligible breast cancer cases as TNBC. These women were more likely to be young, under the age of 40 [odds ratio (OR) 1.53; 95% confidence interval (CI) 1.37–1.70] and non-Hispanic blacks (OR 1.77; 95% CI 1.59–1.97) [14]. A report of the US Surveillance, Epidemiology, and End Results (SEER) program, a large-scale population-based study of incidence rates for major breast cancer subtypes, further lends support to these statistics [16]. Among the 57,483 cases diagnosed in 2010, 6193 (12.2%) are of the TNBC subtype. Non-Hispanic black women were more likely to be diagnosed with TNBC than other racial groups (OR = 2.0, 95% CI 1.8–2.2) [16]. In this study, Hispanics were 30% (OR = 1.3, 95% CI 1.2–1.6) more likely to be diagnosed with TNBC as compared to non-Hispanic whites [16]. Age of onset of TNBC is earlier as compared to ER+/HER2− breast cancers. Those diagnosed with TNBC were 10–30% less likely to be aged 65 years and older [16].

Consistent with data from American studies, a high prevalence of TNBC has been reported in Mexico where patients with breast cancer are reported to be younger at time of disease onset [17, 18]. In a retrospective review of 2074 Hispanic breast cancer patients seen between 1998 and 2008 at the National Cancer Institute in Mexico City, the prevalence of TNBC was 23.1% and in univariate analysis, associated with younger age (49.2 vs. 52.2 years; \( P < 0.001 \)) and premenopausal status (OR, 0.72; 95% CI 0.58–0.88; \( P = 0.002 \)), and the latter remained significantly associated with TNBC diagnosis in multivariate analysis [18]. Elsewhere in the world and similar associations for women of African ancestry have also been shown. A study of 507 breast cancer patients in Nigeria and Senegal reports a low mean age of 44.8 years at diagnosis and a majority of tumors being TNBC subtype (27%) [19, 20].

### 2.2.2 Socioeconomic Status

Typically, the percentage of all breast cancers increases as socioeconomic status increases [14]. However, low socioeconomic status has been associated with breast tumors which are of high-grade, high clinical stage, and ER-negative status. Studies have reported higher odds of TNBC with lower socioeconomic status with some suggestions that the higher odds for TNBC in minority race or ethnic groups is explained by difference in socioeconomic status. Women in areas of low socioeconomic status from the California Cancer Registry were more likely than women living in areas of high socioeconomic status to be diagnosed with TNBC [14].

In a study using data from the National Cancer Data Base (NCDB), a national hospital-based cancer registry involving 260,577 breast cancer cases, the odds of TNBC subtype in minority populations stratified by socioeconomic status was estimated and reported [21]. Consistent with previous results, non-Hispanic blacks had a 1.84 times greater odds (OR = 1.84; 95% CI 1.77–1.92) of having TNBC subtype vs. hormone receptor-positive, HER2-negative subtype compared with
TNBC was also higher in uninsured and Medicaid-insured patients as compared to patients with other insurance types [21]. Patients with low socioeconomic status had a higher proportion of TNBC subtype than other patients and a 1.14 times higher odd of being diagnosed with TNBC subtype (OR = 1.14; 95% CI 1.08–1.19) [21]. In this study, the effect of race or ethnicity of having TNBC is evident even after controlling for difference in socioeconomic status suggesting a role for other factors in the odds differences.

2.2.3 BRCA Mutations

Approximately 5–10% of newly diagnosed breast cancers are attributed to hereditary causes. BRCA1 and BRCA2 gene mutations are associated with a 40–60% lifetime risk of female breast cancers [22, 23]. In the general population, deleterious BRCA1 or 2 mutation rates are approximately 1 in 400 to 1 in 800 people [24]. The prevalence of BRCA mutations differs by population groups and ethnicity. For example, approximately 10% of Ashkenazi Jewish women with breast cancer carry a founder mutation in BRCA1 or BRCA2 [25, 26]. In a large cross-sectional analysis of 46,276 individuals tested for mutations in BRCA1 and BRCA2 genes, women of African ancestry had the highest prevalence of deleterious mutations (15.6% vs. 12.1% for Western European, OR 1.3 (1.1–1.5)) [24]. This group is followed closely by women of Latin American ethnicity with a prevalence of 14.8% vs. 12.1% for Western European (OR 1.2, 95% CI 1.1–1.4). In both groups, the number of BRCA1 mutations was twice as many as BRCA2 mutations [24].

It is estimated that 25% of TNBCs carry a BRCA1 mutation, and more than 75% of tumors in women who carry the BRCA gene are of the triple-negative and/or basal-like phenotype [12]. In a retrospective review of 469 subjects with TNBC referred to the hereditary cancer risk clinics at Duke and University of California, San Francisco, 31% tested positive for a mutation in BRCA1, BRCA2, or both genes [27]. In a study examining BRCA mutations in a cohort of young breast and ovarian cancer patients unselected for family history in Mexico, a high prevalence of BRCA mutations (9 out of 33 TNBC, 27%) was reported in women with TNBC. All nine harbored a mutation in the BRCA1 gene [17].

2.2.4 Other Risk Factors: Obesity, Parity, and Breastfeeding

Risk factors of TNBC differ slightly from that of other breast cancer subtypes. In general, a reduction in lifetime exposure to estrogen, long duration of breastfeeding, high parity, and young age at first pregnancy can protect from hormone receptor-positive breast cancers. The risk of TNBC differs slightly and is positively associated with higher parity in addition to being negatively associated with duration of breastfeeding [9, 18, 28, 29]. Women with TNBC had younger ages at menarche and at first full-term pregnancy [29]. Kwan et al. report on data from two large prospective breast cancer survivorship studies. Premenopausal TNBC cases were more likely to be overweight [30].
2.3 Clinical Presentation

Primary TNBC tumors are larger, of higher grade, and grow rapidly [9, 13, 14, 16, 31]. TNBC cancers are more often interval cancers occurring between mammographic screening and are clinically detectable at time of diagnosis [13]. The presence of lymph node metastasis at time of diagnosis of TNBC is conflicting. Dent et al. suggest a higher prevalence of lymph node metastasis in TNBC which does not correlate with tumor size; 55% of women with tumors 1 cm and less in their study had at least one positive lymph node [13]. On the other hand, the Carolina Breast Cancer Study reports no association with positive axillary lymph nodes and basal-like subtype [9]. Upon disease recurrence, a higher proportion of patients with TNBC will experience distant recurrence as compared to local recurrence, and few will experience local recurrence before a distant one [13]. Metastatic TNBCs are more likely to involve the viscera such as the lungs and brains and less likely to involve the bones in contrast to their ER-positive counterpart. The majority of patients will present with multiple sites of disease [12, 32].

2.4 Young vs. Older Triple-Negative Breast Cancer

Approximately 21% of breast cancers are diagnosed at age 70 years and older [11]. Typically, an older age of breast cancer diagnosis is associated with ER-positive breast cancers [14, 16]. However, around 15% of breast cancers in older patients are triple-negative [33]. In a SEER database study investigating the survival pattern of elderly TNBC, older TNBC women had tumors with biologically favorable phenotype. Older TNBC patients tended to have a lower likelihood of lymph node metastases (N0, 69.5% vs. 63.8%; \( P < 0.001 \)), lower TNM stage, and lower tumor grade as compared to younger TNBC patients [34]. Consequently, studies have suggested that older patients with TNBC have similar outcomes when compared with their younger counterparts. In a single institution report of 1759 women aged 70 and above with early operable primary breast cancers, 22% of breast cancers in older women (\( \geq 70 \) years old) were of the TNBC subtypes [35]. There was a clear difference in the management pattern where 47% of patients younger than 70 years old received adjuvant chemotherapy following surgery and no older patient received adjuvant chemotherapy [35]. Despite this, there was a non-statistically significant trend toward better survival in older women [35]. The 5-year breast cancer-specific survival in <70 years was 73% compared to 79% in 70 years and older patients [35]. There was no difference in the 5-year local-regional (local recurrence 10% vs. 14%; regional recurrence 9% vs. 14%) and rates of distant metastases (30% vs. 27%) in the younger and older groups, respectively [35].

2.5 Natural History and Prognosis

TNBCs are aggressive tumors which carry a poorer prognosis as compared to their luminal counterpart [13–15]. For example, in the population-based study from the California Cancer Registry, the relative survival of women with TNBC was poorer
as compared to non-TNBC; 77% of women with TNBC were still alive 5 years after diagnosis as compared to 93% for other breast cancers [14]. When compared with women with other breast cancers, women with TNBC had consistently poorer survival for each stage [14]. The median time to death was shorter for patients with TNBC compared to patients with other subtypes [13]. In addition to being more likely to experience distant recurrences, patients with TNBC are also likely to experience recurrences earlier [13]. The mean time to distant recurrence in a cohort of TNBC patients diagnosed at a single institution in Toronto was 2.6 vs. 5 years ($P < 0.0001$) for other tumor types, respectively. The risk of relapse and death for TNBC is highest during the first 3–5 years from diagnosis [9, 13]. After adjusting for known prognostic variables such as age, grade, tumor size, chemotherapy, and nodal status, the risk of death from breast cancer remained higher for TNBC up to 5 years from diagnosis with a hazard ratio of 1.8 (95% confidence interval (CI) 1.2–2.6; $P = 0.0005$) [13]. This increase was not observed for the period beyond 5 years after diagnosis. All TNBC deaths occur earlier and within 10 years of diagnosis. In contrast, death from breast cancer in patients with other cancer subtypes continues to accrue for up to 18 years after diagnosis [13]. This pattern of recurrence is illustrated by the BEATRICE trial [36]. To date, this trial has enrolled the largest cohort of TNBC patients and evaluates the use of 1 year of bevacizumab in addition to standard chemotherapy in TNBC. A total of 2591 patients were enrolled from 37 countries, and about two thirds of the patients had node-negative disease. The 3-year invasive disease-free survival (DFS) was 83% with distant recurrence in 11% of patient. The most frequent sites of distant recurrences were the lungs (~30%), liver (15–20%), and bone (~20%). Distant CNS recurrence accounted for approximately 7–12% of distant recurrences. Following metastasis, patients with TNBC have a shorter survival as compared to non-TNBC, and the median survival time from diagnosis of distant metastatic disease was 9 vs. 22 months in the cohort of 1601 patients with breast cancer as reported by Dent et al. [13]. Contemporary TNBC studies have reported a median survival time from diagnosis of metastatic disease of around 1 year which unfortunately remains relatively unchanged for the past decade [32].

### 2.6 Treatment and the Triple-Negative Paradox

There are currently no targeted therapies approved for use in TNBC. Chemotherapy is the mainstay of treatment to which some TNBCs are exquisitely sensitive. Yet, despite sensitivity to chemotherapy, TNBC is still associated with a poor prognosis otherwise described as the triple-negative paradox. In a retrospective cohort study examining the relationship between response to neoadjuvant chemotherapy, long-term end points, and breast cancer subtypes, Carey and colleagues report a high clinical response rate of 85% for TNBC to anthracycline-based chemotherapy as compared to the luminal subtypes with a response rate of 39–58% [37]. Pathological complete response to chemotherapy was significantly higher in TNBC (27%) as compared to the luminal subtypes (7%) [37]. Despite this, there was a significant difference in 4-year distant disease-free survival of 71% (95% CI 51–84%) vs. 82%
The poorer outcome is contributed predominantly by those with residual disease following neoadjuvant chemotherapy who had a worse survival due to high early relapse rates resulting in death [37]. The particularly poor outcomes of TNBC patients with residual cancer post-neoadjuvant chemotherapy lend support to efforts focusing on this challenging group of patients. Notably, CREATE-X, a study of adjuvant capecitabine in HER2-negative breast cancers with residual disease post-neoadjuvant therapy, demonstrated an improvement in 5-year DFS 69.8% vs. 56.1% (HR 0.58; 95% CI 0.39–0.87) and overall survival (OS) 78.8% vs. 70.3% (HR 0.52; 95% CI 0.30–0.90) in the cohort of TNBC patients [38].

Several clinical trials evaluating novel treatment strategies in metastatic TNBC are ongoing. Clinical experience suggests that many women with metastatic TNBC relapse and progress quickly on chemotherapy. In a retrospective chart review of patients with metastatic TNBC who received first-line chemotherapy, duration of first-, second-, and third-line chemotherapy was used as a surrogate for duration of treatment response [32]. The median duration of first-line chemotherapy for all patients was 11.9 weeks (range 0–73.1 weeks), and 78% of patients went on to receive second-line chemotherapy with a median duration of 9 weeks (range 0–120.9 weeks), and 49% received third-line chemotherapy with a median duration of 3 weeks (0–59 weeks) [32]. Multivariate analysis revealed five predictors of survival which included history of previous adjuvant or neoadjuvant chemotherapy (HR 2.77; 95% CI 1.39–5.52; \( P = 0.004 \)), distant disease-free interval >12 months (HR 0.36, 95% CI 0.26–0.83; \( P = 0.01 \)), age >50 at diagnosis of metastatic disease (HR 0.46, 95% CI 0.27–0.76; \( P = 0.003 \)), type of metastatic disease (visceral vs. non-visceral) (HR 1.94; \( P = 0.021 \)), and increased alkaline phosphatase levels (HR 2.4; \( P = 0.002 \)). It is important to take the aggressive and progressive nature of this disease and the short window for therapeutic intervention into account. This represents a challenge in the clinical management of these patients as physicians treat to palliate and extend life and also in the design of clinical trials that either focus or include this poor-risk group. As an example, in KEYNOTE-086, a phase II study of single-agent pembrolizumab, a fully human IgG4 monoclonal antibody that directly blocks the interaction between the T-cell inhibitory molecule programmed death receptor-1 (PD-1) and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), for previously treated metastatic TNBC, 386 patients were screened to enroll 170 patients resulting in a high screen fail rate of more than 50% [39]. Secondly, the high response rates and yet poorer outcomes of TNBC calls to question the use of response rate as a surrogate end point. Finally, with technological advances in interrogating the genome, transcriptome, and proteome, we see a shift in the paradigm of cancer care as we move toward precision medicine. Novel trial designs such as umbrella and basket trials can enroll patients with companion molecular marker testing and assess the efficacy of treatment for the identified marker. An important goal in all trials is to identify prognostic and predictive factors to reliably select TNBC patients for different treatment approaches. Important limitations of studying this poor-risk population need to be overcome, and identifying TNBC patients for select trial needs to be performed expeditiously and ideally early during the course of their metastatic disease.
Conclusion

The natural history of TNBC has been described over the past 15 years consequent to the refinement of breast cancer subtypes. Moving forward, integration of molecular data will shed light on the TNBC subtype biology as well as treatment for early and late disease. At the individual patient level of care, what is needed is to integrate the pathological, clinical, and molecular data with encouragement of enrollment onto clinical trials to optimize care. Additionally, increasing attention to germline risk factors for the development of TNBC will enhance early detection and improve survival.

References


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