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Original Research

# Histologic heterogeneity of triple negative breast cancer: A National Cancer Centre Database analysis☆

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Invasive lobular carcinoma;

**Abstract** ***Background:*** Triple negative breast cancer (TNBC) is an aggressive disease, but recent studies have identified heterogeneity in patient outcomes. However, the utility of histologic subtyping in TNBC has not yet been well-characterised. This study utilises data from the National Cancer Center Database (NCDB) to complete the largest series to date investigating the prognostic importance of histology within TNBC.

***Methods:*** A total of 729,920 patients (pts) with invasive ductal carcinoma (IDC), metaplastic breast carcinoma (MBC), medullary breast carcinoma (MedBC), adenoid cystic carcinoma (ACC), invasive lobular carcinoma (ILC) or apocrine breast carcinoma (ABC) treated between 2004 and 2012 were identified in the NCDB. Of these, 89,222 pts with TNBC that received surgery were analysed. Kaplan–Meier analysis, log-rank testing and multivariate Cox proportional hazards regression were utilised with overall survival (OS) as the primary outcome.

***Results:*** MBC (74.1%), MedBC (60.6%), ACC (75.7%), ABC (50.1%) and ILC (1.8%) had significantly different proportions of triple negativity when compared to IDC (14.0%, $p < 0.001$). TNBC predicted an inferior OS in IDC ($p < 0.001$) and ILC ($p < 0.001$). Lumpectomy and radiation (RT) were more common in MedBC (51.7%) and ACC (51.5%) and less common in MBC (33.1%) and ILC (25.4%), when compared to IDC (42.5%, $p < 0.001$).

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Prognosis

TNBC patients with MBC (HR 1.39, p < 0.001), MedBC (HR 0.42, p < 0.001) and ACC (HR 0.32, p = 0.003) differed significantly in OS when compared to IDC.
***Conclusion(s):*** Our results indicate that histologic heterogeneity in TNBC significantly informs patient outcomes and thus, has the potential to aid in the development of optimum personalised treatments.


## 1. Introduction

Triple negative breast cancer (TNBC), defined as breast cancer lacking oestrogen and progesterone receptor expression and a non-amplified human epidermal growth factor receptor (HER-2), represents about 15–25% of breast cancer cases [1,2]. TNBC represents an aggressive subtype, with higher grade and more advanced stage at presentation [2]. These patients have a higher risk of developing both local recurrence and distant metastasis, and because these tumours are insensitive to antihormonal treatment or Her-2 targeted therapies, TNBC patients with metastatic disease have a poor prognosis [2–4].

In addition to locoregional treatment, the standard of care for TNBC is combination chemotherapy [5]. Although TNBC has higher rates of pathologic complete response to neoadjuvant chemotherapy (35–50%), most patients have residual disease and especially a poor prognosis [6]. This difference in response to therapy has been attributed to the heterogeneity of TNBC and improving treatment success will require patient stratification [7–9].

Utilising gene expression analysis, six distinct molecular subtypes of TNBC have been identified (basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like and luminal androgen receptor), and these subtypes are associated with chemotherapy response [1,10]. Although most (around 80%) of TNBC cases classify as the basal-like subtype, these terms are not synonymous, as only 46% of basal-like tumours are triple negative [11,12]. In addition, in a study defining molecular subtypes, only invasive ductal carcinomas (IDC) were analysed, excluding other rare histologic subtypes [13].

Although the vast majority of TNBC is classified as IDC, histologic subtyping has been used to further stratify prognosis [14–18]. Certain rare histologic subtypes within TNBC, such as adenoid cystic carcinoma (ACC), have better outcomes, while others, such as metaplastic breast carcinoma (MBC), are associated with particularly dismal outcomes [15,18–20]. However, the current literature describing these rare histologies is scarce, especially within TNBC.

In the largest series to date, we analysed data from the National Cancer Center Database (NCDB) to further investigate the heterogeneity of different TNBC histologies with respect to clinicopathologic features and treatment approaches.

## 2. Patients and methods

The NCDB registry was used to identify study subjects diagnosed between 2004 and 2012. The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It is a hospital-based registry that represents 70% of all cancer cases in the United States, drawing data from more than 1500 commission-accredited cancer programs. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data.

A total of 729,920 patients diagnosed with breast cancer were initially identified across six histological subtypes, including invasive ductal carcinoma (IDC), metaplastic breast carcinoma (MBC), medullary breast carcinoma (MedBC), adenoid cystic carcinoma (ACC), invasive lobular carcinoma (ILC) and apocrine breast carcinoma (ABC). Of these patients, 96,415 patients were diagnosed with TNBC. These six histologic subtypes were chosen because they had the highest number of cases with confirmed TNBC within the database. Because the vast majority of patients received surgical treatment of the primary site (>92%), we excluded all those patients who did not receive surgery from our analysis, of which a total of 89,222 patients across the six histologic subtypes of interest remained.

Our primary outcome was overall survival (OS), defined as the number of months from the patient's date of diagnosis to their date of death, loss to follow-up or last date available (December 31, 2012). Patient characteristics were gathered from the NCDB, and these included patient age, race, health insurance status, Charles/Deyo score, tumour size, grade, pathologic stage and lymphovascular invasion. Treatment characteristics included in our study were primary site surgery, surgical margin status, regional nodal status, chemotherapy and radiotherapy. In addition, the time