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ORIGINAL ARTICLE

Pattern of Recurrence and Survival Outcomes in Non-Metastatic Triple-Negative Breast Cancer; A Retrospective Analysis

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OBJECTIVE

Triple-negative breast cancer (TNBC) is an aggressive heterogeneous cancer and carries poor prognosis. The study was conducted to analyze the recurrence pattern and survival outcome in TNBC patients.

METHODS

A retrospective analysis was performed for 171 consecutive non-metastatic TNBC patients. Chi-square test, Kaplan-Meier method, and Cox-regression analysis were used for statistical analysis. P<0.05 was considered significant.

RESULTS

Patients were diagnosed commonly at younger age (64.8% patients were ≤50 years, with median age of 48 years), and node-positive (60.2%) disease. At a median follow-up of 40 months, recurrence was observed in 35.7% of patients. The cumulative recurrence rate at 1 year, 2 years, 3 years were 9.4%, 26.3%, and 33.9% respectively. Distant metastasis (73.8%) and multiple lesions (86.9%) were the most common pattern of recurrence. Common sites of recurrences in decreasing order were lung > nodes (regional+non regional) > brain > bone > liver > contralateral breast. The disease-free survival (DFS) and overall survival (OS) were 64.3% and 78.4%, respectively. High-grade tumor, nodal metastasis, <10 number of lymph node dissection (LND) were independently associated with poor DFS, whereas the presence of nodal metastasis was the single factor associated with poor OS.

CONCLUSION

TNBC is common in younger age and node-positive disease. Recurrence occurs commonly at distant sites as multiple lesions in the first 3 years of diagnosis. High-grade tumor, <10 LND, and nodal metastasis are associated with poor DFS, whereas nodal involvement is associated with poor OS.

Keywords: Breast cancer; metastasis; pattern; recurrence; survival; triple negative.

Introduction

Breast cancer ranks first in incidence and cancer-associated death among women, both in India as well as worldwide.[1] The age-adjusted incidence rate of breast cancer is increasing in different parts of India. [2] Breast cancer has heterogeneous tumor biology, which confers variable treatment response and clinical outcomes.[3,4] Molecular subtyping of breast cancer is based on differential overexpression of surface proteins. Based on the estrogen receptors (ER), the progesterone receptors (PR), the human epidermal

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Table 1 Clinicopathological characteristics

Parameters	n	%
Age (in years)		
Median	48	
Range	24-85	
≤50 years	103	60.2
>50 years	68	39.8
Menopausal status		
Premenopausal	77	45
Postmenopausal	94	55
Family history		
Positive	5	2.9
Negative	166	97.1
Side		
Right	84	49.1
Left	86	50.3
Bilateral	1	0.6
Histopathology		
Invasive ductal	162	94.7
Metaplastic	5	2.9
Medullary	4	2.3
Grade		
I	8	4.7
II	98	57.3
III	65	38.0
Lymphovascular invasion		
Present	23	13.5
Absent	148	86.5
Tumor stage		
T1	13	7.6
T2	98	57.3
T3	40	23.4
T4	20	11.7
Nodal stage		
N0	75	43.9
N1	51	29.8
N2	27	15.8
N3	18	10.5
Stage Group		
Stage I/II	69	40.4
Stage III	102	59.6
Margin status		
Positive	7	4.1
Negative	164	95.9

growth factor receptors-2 neu (HER-2μ) protein expressions, it is classified into; luminal A (ER positive, HER-2μ negative), luminal B (ER positive, HER-2μ positive), HER-2μ enriched (ER negative, HER-2μ positive), and triple negative or basal like (ER negative and HER-2μ negative).[5,6] Triple-negative breast cancer (TNBC) comprises a diverse group of breast tumor having aggressive biology with a higher rate of recurrence and poorer survival in spite of its higher chemosensitivity compared to the other breast cancer subtypes, due to lack of targeted therapy.[7-9] In view of limited data on survival in Indian patients, the present study was conducted to analyze the recurrence pattern and the survival in TNBC patients.

Table 2 Treatment and outcome characteristics

Parameters	n	%
Surgery		
MRM	166	97.1
BCS	5	2.9
Nodal dissection		
≥10 LND	125	73.1
<10 LND	46	26.9
Chemotherapy		
NACT	31	18.1
ACT	166	97.1
Chemotherapy regimens		
Anthracycline+taxane	137	80.1
Anthracycline	29	17.0
Platinum+taxane	5	2.9
Radiotherapy		
PMRT	100	58.5
WBRT	5	2.9
Pattern of recurrence		
Loco regional	16	26.2
Distant	45	73.8
Total	61	100
Sites of recurrences		
Lung	34	55.7
Nodes	17	27.9
Brain	13	21.3
Bone	12	19.7
Liver	7	11.5
Contralateral Breast	4	6.6
Total	61	100
Number of recurrences		
Solitary recurrence	8	13.1
Multiple recurrence	53	86.9

MRM: Modified Radical Mastectomy; BCS: Breast conservation surgery; LND: Lymph node dissection; NACT: Neo adjuvant chemotherapy; ACT: Adjuvant chemotherapy; PMRT: Post mastectomy radiotherapy; WBRT: Whole breast radiotherapy

Materials and Methods

A retrospective analytical study was performed for consecutive 171 newly diagnosed TNBC patients treated between January 2014 and May 2019, at a tertiary care cancer center in South India. Information was retrieved from the cancer registry, after obtaining the

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Table 3 Factors affecting recurrence free survival and overall survival in non metastatic TNBC patients evaluated by multivariate analysis (Cox proportional hazard model)

Factors	DFS		OS	
	P	HR (95%CI)	P	HR (95%CI)
Age		1.23		1.85
≤50 years	0.469	(0.70-2.12)	0.099	(0.89-3.85)
>50 years				
Histopathology		0.326		
IDC	0.179	(0.06-1.67)	0.339	0.47
Metaplastic				(0.10-2.20)
Medullary				
Grade		1.76		
I	0.026	(1.07-2.88)		1.24
II			0.521	(0.64-2.43)
III				
Tumor size				
T1		1.41		1.23
T2	0.062	(0.98-2.03)	0.359	(0.79-1.91)
T3				
T4				
Nodal status		4.22		4.58
Negative	0.002	(1.73-10.28)	0.027	(1.19-17.61)
Positive				
Prognostic Stage		0.63		3.19
I/II	0.349	(0.24-1.64)	0.152	(0.65-15.62)
III				
Margin status		1.32		2.79
Positive	0.660	(0.38-4.53)	0.191	(0.60-12.96)
Negative				
LVI		0.74		0.85
Present	0.384	(0.38-1.45)	0.720	(0.37-1.99)
Absent				
LND		2.56		1.97
≥10	0.001	(1.49-4.40)	0.074	(0.94-4.15)
<10				

DFS: Disease free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; IDC: Invasive ductal carcinoma; LVI: Lymphovascular invasion; LND: Lymph node dissection

permission from Institutional Ethical Committee, and the study was performed in accordance with the declaration of Helsinki. The study was aimed to evaluate the recurrence pattern, survival outcome, and factors affecting disease-free survival (DFS) and overall survival (OS). Information of each patient including clinicopathology, treatments received, disease status, and follow-up information was noted in a pre-designed proforma. The follow-up data were updated by phone calls using the contact numbers noted in the registry. All cases were diagnosed histopathologically, and molecular sub-typing was done using immunohistochemistry (IHC) study. IHC result of 1+ score for HER-2μ was considered negative and 2+ score was further tested with fluorescence in-situ hybridization (FISH). TNBC was defined as patients with ER/PR negative in IHC (<1% expression), and negative for HER-2μ (1+ score in IHC/ negative result in FISH). The staging classification and prognostic stage grouping was based on the AJCC TNM staging (8th edition).[10] Data were collected for total of 179 patients, out of which 8 patients did not complete the planned treatment and were removed from analysis. DFS was defined by the duration from start of primary treatment to the date of disease recurrence or death. The OS was defined as the time from the date of initiation of primary treatment to the date of death. Six patients were lost to follow up after certain duration and failed to communicate over

phone call were considered censored.

Statistical Analysis

IBM SPSS statistics for windows, version 22.0 (Armonk, NY: IBM Corp) was used for statistical analysis. The association between categorical variables was analyzed using Chi-square test. Survival analysis was performed using the Kaplan Meier method and was compared between different factors using Log-Rank (Mantle-Cox) testing. P<0.05 was considered statistically significant. The factors affecting OS and DFS were evaluated by multivariate analysis using Cox proportional hazard regression model (with P<0.05 and 95% confidence interval).

Results

Total 171 consecutive non-metastatic TNBC patients were analyzed for clinicopathological characteristics, recurrence, and survival pattern. The clinicopathological characteristics and outcome characteristics are depicted in Tables 1 and 2, respectively. The median age at diagnosis was 48 years with majority of patients belonged to <50 years of age. Invasive ductal cancer and intermediate-grade were the most common histopathological subtype. Majority of patients had tumor size of more than 2 cm size (92.4%), nodal involvement (56.1%). Most of the patients underwent modified radical mastectomy (97.1%), ≥10 lymph node dissection (LND) (73.1%), and adjuvant chemotherapy (97.1%). Pathological T and N staging were considered for eighty-two percent of patients, who underwent primary modified radical mastectomy or breast conservation surgery (BCS) with axillary staging. Whereas the remaining patients who underwent neoadjuvant chemotherapy, the pre-chemotherapy clinical staging was considered. Five patients with clinical T1/T2 and N0/N+ disease underwent BCS with sentinel lymph node biopsy (SLNB), out of which two patients found SLNB positive and subsequently underwent level I and II axillary LND. Chemotherapy used most commonly was anthracycline plus taxane-based regimen (80.1%), post-mastectomy radiotherapy was given in 58.5% of patients. At a median follow-up of 40 months, approximately one-third of the total patients developed recurrence. Most of the recurrences (95%) occurred in the first 3 years of primary treatment. Out of the total recurrences, three fourth of patients had distant recurrence and commonly had multiple lesions at recurrence (Table 2). Common sites of recurrences were lung > nodes (regional+non regional) > brain > bone > liver > contralateral breast (Table 2). Multivariate analysis showed the factors associated with poor DFS were high grade tumor (p=0.026), <10 LND (p=0.001), nodal positivity (p=0.002), whereas nodal positivity was associated with poor OS (p=0.027) (Table 3). The difference in time trend of DFS and OS based on the associated factors are depicted in the Kaplan Meier curve (compared by log-rank test-

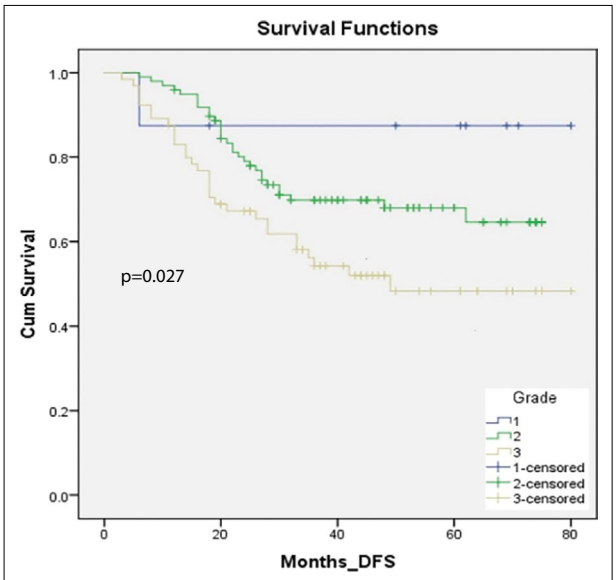

Fig. 1. Difference in disease free survival based on different tumor grades.
DFS: Disease-free survival.

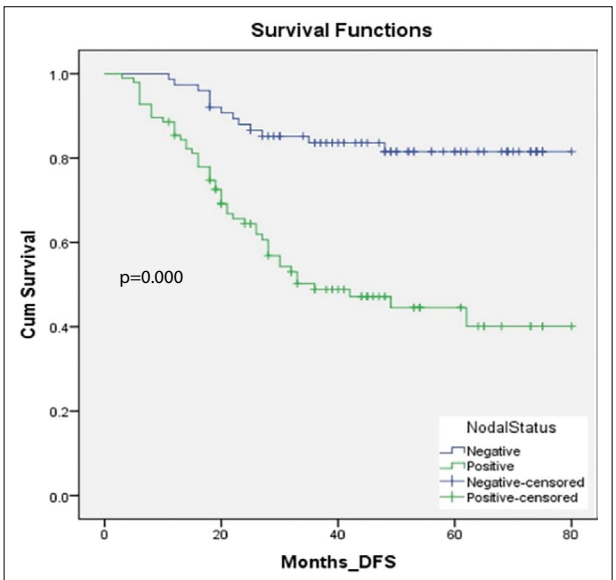

Fig. 2. Difference in disease free survival based on nodal involvement.
DFS: Disease-free survival.

Turk J Oncol 2022;37(2):122–28
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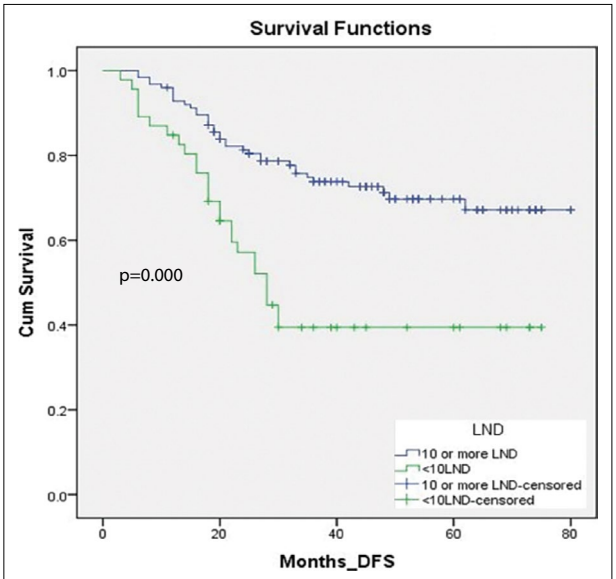

Fig. 3. Difference in disease free survival based on number of lymph node dissection.
LND: Lymph node dissection.

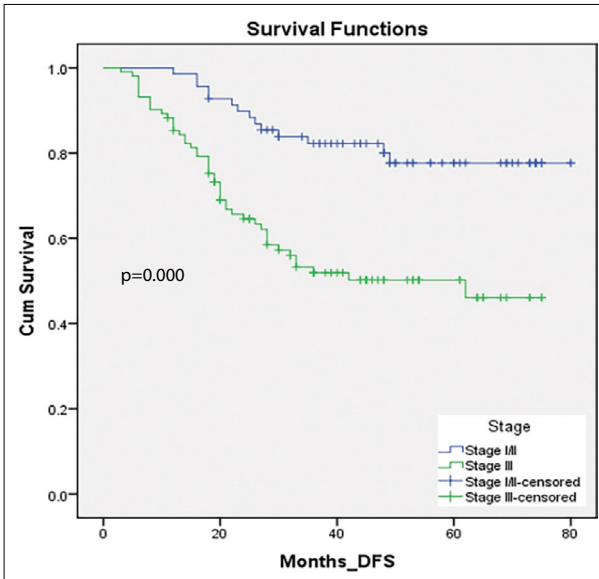

Fig. 5. Difference in disease free survival based on stage groups.
DFS: Disease free survival.

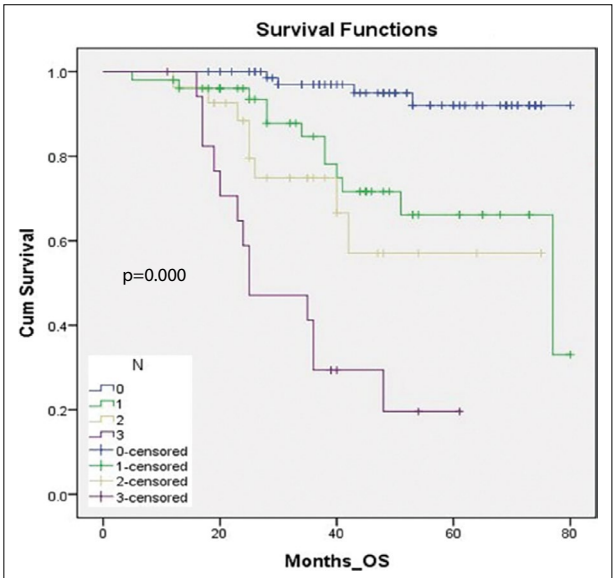

Fig. 4. Difference in overall survival based on nodal involvement.
OS: Overall survival.

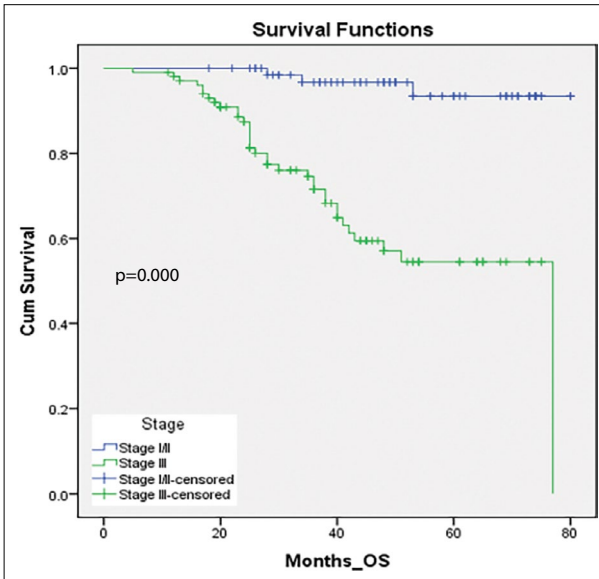

Fig. 6. Difference in overall survival based on stage groups.
OS: Overall survival.

ing) in the Figures 1-4. Kaplan Meier survival analysis with log-rank testing found that OS and DFS in stage I/II breast cancer were significantly better (p=0.000) compared to the stage III breast cancer. The 5 year OS was 93% vs. 54%, whereas DFS was 78% versus 48% in stage I/II and stage III breast cancer patients, respectively (Figs. 5, 6).

Discussion

TNBC is a heterogeneous neoplasm with marked genetic, transcriptional, histological, and clinical differences.[7-9] The age of diagnosis of TNBC patients is significantly lower compared to non-TNBC patients.[11] TNBC in the present study was more prevalent among

younger (<50 years) patients, which was in concordance with previous study findings.[12-16] The median age of diagnosis in the present study was 48 years, which was in concordance with the previous Indian study finding of Doval et al.,[17] whereas it was lower as compared to the study finding of Pogoda et al.[18] Premenopausal women are associated with a higher incidence of TNBC compared to post-menopausal women;[19] whereas 55% of patients in the present study were postmenopausal, which was in concordance with Ghosh et al.[20] TNBC can be inherited through germ line mutation in BRCA 1 or 2 gene and carriers of these genes have higher risk of developing TNBC.[21] BRCA 1 or 2 gene analysis was not performed in the present study. Family history of breast or ovarian cancer was found in 3.5% of patients, whereas it was reported in 5.4% of patients in a study by Doval et al.[17] TNBC is commonly characterized by high grade, aggressive malignancy and mostly diagnosed in advanced stage.[22-24] Similarly in the present study, most patients had high-grade tumor (38%) and were diagnosed in locally advanced stage (59.6%). TNBC patients are commonly diagnosed with larger tumor size and nodal metastasis.[20,22] The present study findings are in concordance with the above reports; whereas it is contradicting the study finding of Plasilova et al.,[25] which reported TNBC to be associated with larger tumor size, whereas lower rate of nodal metastasis compared to non-TNBC patients. Most patients in the present study underwent modified radical mastectomy followed by adjuvant chemotherapy. The most common pattern of recurrence in our study was at distant sites, which was similar to the previous study findings.[20] Lung was the most common site of distant recurrence followed by brain, bone, liver, and contralateral breast. Previous studies have reported the common sites of distant recurrences were lung, brain, bone, and liver.[26] Brain metastasis was reported to occur in 14% of TNBC patients in the study by Lin et al.,[27] whereas in our study brain metastasis was observed in 21.3% of patients. Most of the recurrences in our study occurred as multiple lesions and within first 3 years of diagnosis.[18,23] Approximately one-third of TNBC patients developed recurrences in our study, which similar to the study finding of Pogoda et al.[18] Distant failure was observed in 73.8% of total recurrences and most recurrences observed by the first 3 years of diagnosis, which was similar to the study finding of Dent et al. and Ghosh et al.[12,20] Factors associated with recurrence as reported in the previous study were larger tumor size, nodal metastasis, advanced stage.[26,28] Previous study had reported the larger tumor size as the only independent factor associated with poor OS,[28] whereas another study had reported nodal metastasis to be the only independent factor associated with poor OS.[29] In the present study high-grade tumor, nodal metastasis, and <10 LND were independently associated with higher risk of recurrence, whereas nodal metastasis alone was independently associated with poor OS.

Conclusion

The present study found TNBC to be common in younger age and higher rate of node positivity. Recurrence occurs commonly at distant sites as multiple lesions, and mostly in the first 3 years of diagnosis. High-grade tumor, <10 LND, and nodal metastasis are associated with poor DFS, whereas nodal involvement is independently associated with poor OS. Development of specific targeted therapy is required to prolong survival in these patients.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.
2. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al; ICMR-NCDIR-NCRP Investigator Group. Cancer statistics, 2020: report from national cancer registry programme, India. JCO Glob Oncol 2020;6:1063–75.
3. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. World J Clin Oncol 2014;5(3):412–24.

Turk J Oncol 2022;37(2):122–28
doi: 10.5505/tjo.2022.3458

4. Rivenbark AG, O'Connor SM, Coleman WB. Molecular and cellular heterogeneity in breast cancer: challenges for personalized medicine. Am J Pathol 2013;183(4):1113–24.
5. Tsang JYS, Tse GM. Molecular classification of breast cancer. Adv Anat Pathol 2020;27(1):27–35.
6. Eliyatkın N, Yalçın E, Zengel B, Aktaş S, Vardar E. Molecular classification of breast carcinoma: from traditional, old-fashioned way to a new age, and a new way. J Breast Health 2015;11(2):59–66.
7. Garmpis N, Damaskos C, Garmpi A, Nikolettos K, Dimitroulis D, Diamantis E, et al. Molecular classification and future therapeutic challenges of triple-negative breast cancer. *In Vivo* 2020;34(4):1715–27.
8. Yin L, Duan JJ, Bian XW, Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res 2020;22(1):61.
9. Lehmann BD, Pietenpol JA. Identification and use of biomarkers in treatment strategies for triple-negative breast cancer subtypes. J Pathol 2014;232(2):142–50.
10. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. Ann Surg Oncol 2018;25(7):1783–5.
11. Qiu J, Xue X, Hu C, Xu H, Kou D, Li R, et al. Comparison of clinicopathological features and prognosis in triple-negative and non-triple negative breast cancer. J Cancer 2016;7(2):167–73.
12. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13(15 Pt 1):4429–34.
13. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 2006;24(36):5652–7.
14. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer 2007;109(9):1721–8.
15. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295(21):2492–502.
16. Morris GJ, Naidu S, Topham AK, Guiles F, Xu Y, McCue P, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Cancer 2007;110(4):876–84.
17. Doval DC, Radhakrishna S, Tripathi R, Kashinath RI, Talwar V, Batra U, et al. A multi-institutional real world data study from India of 3453 non-metastatic breast cancer patients undergoing upfront surgery. Sci Rep 2020;10(1):5886.
18. Pogoda K, Niwińska A, Murawska M, Pieńkowski T. Analysis of pattern, time and risk factors influencing recurrence in triple-negative breast cancer patients. Med Oncol 2013;30(1):388.
19. Dietze EC, Sistrunk C, Miranda-Carboni G, O'Regan R, Seewaldt VL. Triple-negative breast cancer in African-American women: disparities versus biology. Nat Rev Cancer 2015;15(4):248–54.
20. Ghosh J, Agarwal S, Ganguly S, Debkara D, Biswas B, Nandi S, et al. Patterns of recurrence in triple negative breast cancer patients (automated IHC): an Indian tertiary care center data. J Clin Oncol 2018;36(15):suppl–e13128.
21. Chen H, Wu J, Zhang Z, Tang Y, Li X, Liu S, et al. Association between BRCA status and triple-negative breast cancer: a meta-analysis. Front Pharmacol 2018;9:909.
22. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol 2016;13(11):674–90.
23. Alluri P, Newman LA. Basal-like and triple-negative breast cancers: searching for positives among many negatives. Surg Oncol Clin N Am 2014;23(3):567–77.
24. Fayaz MS, El-Sherify MS, El-basmy A, Zlouf SA, Nazmy N, George T, et al. Clinicopathological features and prognosis of triple negative breast cancer in Kuwait: A comparative/perspective analysis. Reports Pract Oncol Radioth 2014;19(3):173–81.
25. 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.
26. Steward L, Conant L, Gao F, Margenthaler JA. Predictive factors and patterns of recurrence in patients with triple negative breast cancer. Ann Surg Oncol 2014;21(7):2165–71.
27. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer 2008;113(10):2638–45.
28. Eralp Y, Kılıç L, Alço G, Başaran G, Doğan M, Dinçol D, et al. The outcome of patients with triple negative breast cancer: The Turkish Oncology Group Experience. J Breast Health 2014;10(4):209–15.
29. Mousavi SA, Kasaeian A, Pourkasmaee M, Ghavamzadeh A, Alimoghaddam K, Vaezi M, et al. Assessing the prognostic factors, survival, and recurrence incidence of triple negative breast cancer patients, a single center study in Iran. PLos One 2019;14(1):e0208701.