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Evaluation of Local and Distant Recurrence Patterns in Patients with Triple-Negative Breast Cancer According to Age

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Abstract

Background—Triple-negative subtype (TNBC) and young patient age are both associated with an increased risk of local recurrence (LR) and distant recurrence (DR). In young women with TNBC, it is unclear whether subtype or patient age is driving prognosis.

Methods—Patients treated for primary TNBC from 1998 to 2011 were identified from the breast surgery database. Clinico-pathological characteristics, treatment, and outcomes were compared between patients < 40 and ≥ 40 years of age at diagnosis. Multivariate models were used to identify factors independently associated with LR and DR.

Results—Among 1930 patients with TNBC, 289 (15%) were < 40 and 1641 (85%) were ≥ 40 years of age at diagnosis. Younger patients were more likely to present with higher stage disease and more likely to receive mastectomy ($p < 0.01$), axillary node dissection ($p < 0.01$) and chemotherapy ($p < 0.01$). At a median follow-up of 74 months (0–201.1) there was no difference in LR or disease-free survival (DFS) by age group (5 yr LR = 3.9% (95% CI 1.5–6.2) vs 4.5% (95% CI 3.5–5.6) and 5yr DFS = 75.3% (95% CI 70.2–80.7) vs. 77.7% (95% CI 75.6–79.8), $p = 0.94$) in patients < 40 and ≥ 40 years respectively. On multivariate analysis, larger tumor size, lymphovascular invasion, and nodal positivity were associated with increased risk of DR. Age and type of surgery were not significantly associated with either outcome.

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Conclusion—Young age at diagnosis is not an independent risk factor for LR or DR in patients with TNBC.

Background

The triple-negative breast cancer (TNBC) subtype and young patient age have both been shown to impact breast cancer-specific outcomes¹. Young breast cancer patients experience higher rates of local and distant recurrence when compared to their older counterparts; yet they also frequently present with TNBC, a particularly aggressive breast cancer subtype associated with inferior outcomes²⁻⁴. Given the overlapping risk factors of young age and triple-negative subtype in young women with TNBC, it is unclear whether patient age or subtype is driving prognosis. Here, we examine outcomes in a large population of patients with TNBC according to age.

Methods

Patient selection

All female patients treated for primary TNBC between January 1998 and December 2011 in the Department of Surgery at Memorial Sloan Kettering Cancer Center (MSKCC) were retrospectively identified by analysis of a prospectively maintained service database. Exclusion criteria were incomplete information about receptor status and stage IV disease at diagnosis. Treatment and outcome variables were abstracted from medical records. Triple-negative subtype was defined by the absence of estrogen receptor (ER) and progesterone receptor (PR) expression by immunohistochemistry (IHC), and the lack of HER2 overexpression by IHC, +/- a ratio of <2.0 by FISH. The study was approved by the MSKCC institutional review board.

Endpoints and statistical analyses

Local recurrence (LR) was defined as ipsilateral breast or chest wall recurrence; regional recurrence (RR) as ipsilateral axillary, internal mammary or supraclavicular lymph node recurrence; and distant recurrences (DR) were captured as single distant recurrence (visceral, lymph node [mediastinal, thoracic, cervical], brain, and bone) or multiple site recurrence. Charts were reviewed for date and disease status at last follow-up (no evidence of disease, alive with disease, died of disease, died of other cause, or died of unknown cause). Disease-free survival (DFS) was defined as the time from date of diagnosis to diagnosis of LR, RR, or DR or death and censored at date of last follow-up.

Univariate comparisons were made between patients < 40 and ≥ 40 years of age at diagnosis using chi-squared tests, Fisher's exact tests and Wilcoxon rank-sum tests. LR, RR and DR were treated as competing events and when more than one type of recurrence occurred on the same day, the event was counted as the most serious type of recurrence. Death without recurrence was a competing event and follow-up was censored at the time of last follow-up for patients who were alive and recurrence free. Cumulative incidence of LR and DR were estimated using competing risks methodology and compared using Gray's test. Multivariate Fine and Gray regression was used to examine whether age was independently associated with local and regional recurrences. Both models were adjusted for tumor size, grade

(histologic and nuclear), type of surgery, lymphovascular invasion (LVI), chemotherapy, radiation, and nodal status. DFS was compared between groups with a log-rank test. Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, NC, USA) and R (R Foundation, Vienna, Austria) with the survival and cuminc packages and p values of < 0.05 were considered statistically significant.

Results

We identified a total of 1971 patients treated for primary TNBC. Ten patients presented with stage IV disease and 31 had incomplete receptor status information and were excluded, leaving a total of 1930 patients who met the study criteria. Clinical, pathologic, and treatment variables are shown in Table 1. Median patient age was 54 years (19-95 years). At time of diagnosis, 289 (15%) patients were < 40 and 1641 (85%) were ≥ 40 years of age. Patients < 40 years old were more likely to present with larger tumors (median 2.0 vs. 1.7, $p < 0.01$), which were of higher nuclear ($p < 0.01$) and histologic grade ($p < 0.01$) and were more likely to have positive lymph nodes (47% vs. 37%, $p < 0.02$) (Table 1). Younger patients were also more likely to receive mastectomy (61% vs. 42%, $p < 0.01$), axillary dissection (51% vs. 40%, $p < 0.01$) and chemotherapy (94% vs. 82%, $p < 0.01$) (Table 1).

On univariate analysis, rates of LR (5 yr LR 3.9% [95% CI 1.5-6.2] and 4.5% [95% CI 3.5-5.6]) and RR (5 yr RR 1.9% [95% CI 0.2-3.5] vs. 1.8% [95% CI 1.1-2.5]) were low and did not differ significantly between patients < 40 years and ≥ 40 years (Table 2). Rates of local recurrence also did not significantly differ by age within each surgical procedure (Table 3). 5-year LR rates among patients having breast conserving therapy (BCT) were 2.3% (95% CI 0.3-4.5) for patients < 40 years vs. 4.5 (95% CI 2.9-6.2) for patients ≥ 40 years, and for those having mastectomy, 6.4 (95% CI 1.3-11.4) vs. 4.5 (95% CI 3.1-5.9) respectively.

In contrast, the 5-year cumulative incidence of DR was significantly higher for younger patients compared to older patients (5 yr DR 17.9% [95% CI 13.2-22.5] vs. 11% [95% CI 9.4-12.6], $p < 0.01$). However, at a median follow-up of 74 months (0-201.1), there was no difference in disease-free survival (DFS), between the two age groups (5 yr DFS 75.3% [95% CI 70.2-80.7] vs. 77.7% [95% CI 75.6-79.8], $p = 0.94$) (Table 2).

On multivariate analysis, when adjusting for tumor characteristics and treatment, there was no correlation between the assessed parameters and an increased risk of LR whereas larger tumor size, LVI, and nodal positivity were associated with increased risk of DR (Table 4). Age and type of surgery were not significantly associated with either outcome.

Discussion

A diagnosis of TNBC is associated with an increased risk of locoregional recurrence, an early peak of any recurrence in the first two to three years after diagnosis, and inferior clinical outcomes when compared to other breast cancer subtypes⁵⁻⁷. Young age at diagnosis is also associated with an unfavorable prognosis⁸. Data assessing differences in age-dependent prognosis in TNBC patients are limited and have yielded conflicting results^{9,10}.

In our large cohort of patients with TNBC treated at a single institution, age was not independently associated with LR, DR, DFS or BCSS.

Two large Korean registry-based studies found similar results when looking at outcomes based on breast cancer subtype in patients < 35 and ≥ 35 years of age. Among 2474 patients with primary breast cancer, Kim et al. reported statistically significant lower 5-year relapse-free survival (RFS) rates in younger patients compared to older patients for all subtypes except TNBC⁹. Similarly, when comparing outcomes of 9885 patients diagnosed with primary breast cancer according to age¹¹, Anh et al. found worse overall survival (OS) and BCSS for young patients with hormone receptor positive breast cancer, but not for patients with TNBC. More recently, Partridge et al. reported an increased risk of breast cancer death among women under 40 years of age with luminal tumors whereas in the subset with HER2-type or triple-negative breast cancer, there was no clear increased risk of breast cancer mortality¹².

A recent population-based analysis of women < 50 years of age assessed the impact of age and adjuvant treatment advances across breast cancer subtypes^{13,14}. Among 1101 women <50 years of age treated between 1986 and 1992, and 1945 women treated between 2004 and 2007, Sheridan et al. reported lower RFS and OS in patients <40 years of age for both time cohorts in luminal breast cancers¹³. The same association was present in HER2-positive cancers, but only during the first time cohort in the absence of directed HER2 therapy. In the TNBC subgroup, neither RFS nor OS were associated with age at diagnosis in either time cohort.

In contrast, when examining the effect of age on prognosis in 1732 patients with primary TNBC treated between 1982-2008 at a single institution, Liedtke et al. reported lower DFS, distant DFS, and OS rates in patients < 40 years of age compared to older patients¹⁰. However, because Liedtke's study included patients diagnosed from 1982 onwards and only 119 (33%) of 366 patients < 40 years of age received today's standard anthracycline and taxane based chemotherapy, these results have to be interpreted cautiously.

Similar to our results, Liedtke et al. found that younger patients with TNBC were more likely to present with high grade tumors of higher disease stage and with positive lymph nodes¹⁰. Unlike age at diagnosis, these clinico-pathologic factors were associated with a higher incidence of LR and DR on multivariate analyses in our study. Similar to Liedtke et al., we found a higher 5-year cumulative incidence of distant metastases in patients <40 years of age but this difference was no longer significant on multivariate analysis, and therefore, may be explained by the more advanced clinical stage at first diagnosis in the younger cohort.

Multiple studies have shown an increased risk of LR in TNBC compared to other breast cancer subtypes^{15,16}. Lowery et al. conducted a meta-analysis of 12,592 patients from 15 studies with a median follow-up of 57 months and compared LR rates in patients with primary luminal (ER+/PR+/HER2/neu+/-), triple-negative (ER-/PR-/HER2/neu-), and HER2/neu overexpressing (ER-/PR-/HER2/neu+) breast cancer subtypes¹⁷. Among 7174 women treated with BCT, LR rates were 5% for luminal, 13.5% for triple-negative and

15.7% for HER2/neu positive patients. More recent studies have reported significant reductions in LR for luminal and HER2/neu positive breast cancer subtypes as a result of improvements in endocrine and anti-HER2 therapy¹⁸⁻²⁰; however, LR rates for triple-negative tumors remain higher.

In our cohort 5-year LR rates were much lower than reported by others, 3.9% (95% CI 1.5-6.2) in patients < 40 years and 4.5 % (95% CI 3.5-5.6) in patients ≥ 40 years of age. Improved outcomes in our study may reflect differences in systemic treatment. The meta-analysis conducted by Lowery et al included 15 studies with patients treated between 1980 and 2008 and did not include detailed information about the receipt of chemotherapy or chemotherapeutic regimens. Hence, the LR rate of 13.5% for TNBC patients in the meta-analysis cannot be directly compared to a contemporarily treated TNBC population like ours in which 84% of patients received chemotherapy.

Given the inferior outcomes of patients with TNBC, some have questioned whether or not more extensive surgery can overcome the aggressive biology of TNBC. Several studies have explored this question by comparing mastectomy and BCT outcomes in terms of LR and DR, DFS, and BCCS in TNBC patients; and all report no difference in outcomes by surgical procedure²¹⁻²³. It has also been demonstrated that in the setting of BCT, margin width has no impact on LR²⁴. Although our data demonstrate that rates of LR in TNBC have likely decreased with advances in systemic therapy, rates of LR in TNBC are still higher than in non-TNBC subtypes, and concern has been raised for young patients treated with BCT. We examined rates of LR by age in patients with TNBC according to type of surgery and found no differences in LR rates in patients treated with BCT < 40 years vs. ≥ 40 years of age. Additionally on multivariate analysis type of surgery was not associated with development of LR or DR. Our findings now add to the accumulating evidence demonstrating that young patients with TNBC treated with BCT have similar outcomes to those treated with mastectomy and as such, young age should not be a contraindication for BCT²⁴⁻²⁷.

In contrast to rates of LR, we did observe higher rates of DR in the younger group, yet this observation did not translate into inferior DFS. This finding seems contradictory at first, but can be explained by the fact that although DR was more common in younger patients, death without DR was more common in older patients. Thus when viewed in terms of competing events, there are no significant differences in DFS between the two age groups.

To the best of our knowledge this is the largest single institution study assessing the impact of age at diagnosis on clinical outcomes in patients with TNBC. However, our study is limited by the retrospective nature and incomplete information on BRCA mutation status in the majority of patients. There is a strong association between BRCA mutation status and breast cancer subtype, with 70–90% of BRCA1 mutation-associated breast cancers being TNBC and 8-30% of TNBC harboring a BRCA1 mutation^{28,29}. Further, BRCA1 mutations have been reported in up to 44% of patients < 40 years of age³⁰ and BRCA 1-associated cancers treated with BCT have been associated with a higher incidence of LR compared to non-BRCA-associated tumors³¹. These considerations should be taken into account when discussing surgical treatment options in BRCA mutation carriers; however, in the absence of

BRCA mutation, young age and TNBC subtype should not be considered as a contraindication to BCT.

Conclusion

Young patients with TNBC are more likely to present with higher stage disease when compared to their older counterparts. However, after adjusting for stage, grade, and treatment, young age is not associated with an increased risk of local or distant recurrence, or with inferior survival outcomes among women with TNBC.

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Synopsis

Young age at diagnosis is not associated with inferior survival outcomes in patients with triple-negative breast cancer.

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Table 1
Clinico-pathological characteristics and treatment outcomes according to age

Characteristics	< 40 years (n=289) N (%)	40 years (n=1641) N (%)	<i>p</i> value
Tumor stage			< 0.01
T1	146 (51 %)	1015 (63 %)	
T2	120 (42 %)	527 (33 %)	
T3	7 (2 %)	26 (2 %)	
T4	4 (1 %)	15 (1 %)	
<i>Missing</i>	12 (4 %)	58 (1 %)	
Tumor size, cm, median (range)	2.0 (0.1-15)	1.7 (0.1-12)	< 0.01
Nodal stage			0.02
N0	154 (53 %)	1026 (63 %)	
N1	97 (34 %)	423 (26 %)	
N2	23 (8 %)	110 (6 %)	
N3	15 (5 %)	78 (5 %)	
<i>Missing</i>	0 (0 %)	4 (0 %)	
Patients with N1, N2 or N3 stage	135 (47 %)	611 (37 %)	0.02
Nuclear grade			< 0.01
Low	1 (0 %)	8 (1 %)	
Intermediate	21 (8 %)	212 (13 %)	
High	252 (87 %)	1320 (80 %)	
<i>Missing</i>	15 (5 %)	101 (6 %)	
Histologic grade			< 0.01
Low	0 (0 %)	9 (1 %)	
Intermediate	10 (4 %)	116 (7 %)	
High	270 (93 %)	1478 (90 %)	
<i>Missing</i>	9 (3 %)	38 (2 %)	
LVI			0.28
Yes	95 (33 %)	477 (29 %)	
No	190 (66 %)	1160 (71 %)	
<i>Missing</i>	4 (1 %)	4 (0 %)	
Histology			0.15
IDC	284 (98 %)	1591 (97 %)	
ILC	2 (1 %)	24 (1 %)	
Other	3 (1 %)	26 (2 %)	
Surgery			< 0.01
BCT	112 (39 %)	954 (58 %)	
Mastectomy	177 (61 %)	687 (42 %)	
Axillary procedure			< 0.01
SLNB	142 (49 %)	984 (60 %)	

Characteristics	< 40 years (n=289) N (%)	40 years (n=1641) N (%)	<i>p</i> value
AD	147 (51 %)	654 (40 %)	
No axillary procedure	0 (0%)	3 (0 %)	
Chemotherapy			< 0.01
Adjuvant	259 (90 %)	1292 (78%)	
Neoadjuvant	12 (4 %)	58 (4 %)	
None	11 (4 %)	239 (15 %)	
<i>Missing</i>	7 (2 %)	52 (3 %)	
RT			< 0.01
Whole breast RT	100 (35 %)	864 (53 %)	
Post mastectomy RT	64 (22 %)	229 (14 %)	
Regional nodal RT	56 (19 %)	206 (13 %)	
No	46 (16 %)	246 (15 %)	
<i>Missing</i>	23 (8 %)	96 (5 %)	

LVI: lymphovascular invasion; IDC: invasiv-ductal carcinoma; ILC: invasiv-lobular carcinoma, BCT: breast conserving therapy; SLNB: sentinelnodebiopsy; AD: axillary dissection, RT: radiotherapy; WBRT: whole breast RT; PMRT: post-mastectomy RT; RNRT: regional nodal RT

Table 2
Local, regional and distant recurrence rates and clinical outcomes according to age

	< 40 years (n=289)	40 years (n=1641)	<i>p</i> value
Local recurrence, N (%)	17 (6 %)	88 (5 %)	
Site local recurrence, N (%)			
Breast	13 (76 %)	57 (65 %)	
Chest wall	4 (24 %)	30 (34 %)	
<i>Unknown</i>	0 (0 %)	1 (1 %)	
Cumulative incidence of local recurrence at 5 years (95% Confidence Interval)	3.9 (1.5-6.2)	4.5 (3.5-5.6)	0.82
Regional recurrence, N (%)	5 (2 %)	37 (2 %)	
Site of regional recurrence, N (%)			
Axilla	3 (60 %)	23 (62 %)	
Supraclavicular LN	0 (0 %)	9 (24 %)	
Intramammary LN	2 (40 %)	5 (14 %)	
Cumulative incidence of regional recurrence at 5 years (95% Confidence Interval)	1.9 (0.2-3.5)	1.8 (1.1-2.5)	0.57
Distant recurrence, N (%)	49 (17 %)	189 (12 %)	
Site of first distant recurrence, N (%)			
Multiple sites	17 (36 %)	69 (37 %)	
Visceral	8 (16 %)	48 (25 %)	
LN (mediastinal, thoracic, cervical)	8 (16 %)	19 (10 %)	
Brain	8 (16 %)	25 (13 %)	
Bone	7 (14 %)	21 (11 %)	
Other	1 (2 %)	7 (4 %)	
Cumulative incidence of distant recurrence at 5 years (95% Confidence Interval)	17.9 (13.2-22.5)	11.0 (9.4-12.6)	<0.01
5 year DFS, median (95% Confidence Interval)	75.3 (70.2-80.7)	77.7 (75.6-79.8)	0.94
Median follow-up, month, median (range)	76.1 (0.3-196.1)	73.2 (0-201.1)	0.53

DFS: disease free survival

Table 3
Local recurrence in patients treated with mastectomy vs. BCT according to age

	< 40 years (n=289)	40 years (n=1641)	<i>p</i> value
Subset with mastectomy			
N (%)	177 (61 %)	687 (42 %)	
Site local recurrence			
Breast	0	0	
Chest wall	4 (2 %)	30 (4 %)	
Cumulative incidence of local recurrence at 5 year (95% Confidence Interval)	2.3 (0-4.5)	4.5 (2.9-6.2)	0.2
Subset with BCT			
N (%)	112 (39 %)	954 (58 %)	
Site local recurrence			
Breast	13 (12 %)	57 (6 %)	
Chest wall	0	0	
Unknown	0	1	
Cumulative incidence of local recurrence at 5 years (95% Confidence Interval)	6.4 (1.3-11.4)	4.5 (3.1-5.9)	0.06

BCT: breast conserving therapy

Table 4
Multivariate model for local and distant recurrence adjusted for age, tumor size, grade, surgery type, LVI, chemotherapy, radiotherapy, and LN status

Variable	<i>Local Recurrence</i>		<i>Distant Recurrence</i>	
	Hazard ratio (95% Confidence Interval)	<i>p</i> value	Hazard ratio (95% Confidence Interval)	<i>p</i> value
Age at diagnosis (< 40 years vs. 40 years)	0.91 (0.48-1.75)	0.79	1.38 (0.99-1.95)	0.06
Type of surgery (Mastectomy vs. BCT)	0.62 (0.32-1.18)	0.15	0.99 (0.67-1.45)	0.95
Tumor size (hazard ratio per cm increase)	1.03 (0.88-1.2)	0.74	1.19 (1.10-1.30)	< 0.001
Histologic grade (Grade 3 vs. grade 1 or 2)	0.61 (0.31-1.21)	0.16	1.22 (0.64-1.97)	0.69
Nuclear grade (Grade 3 vs. grade 1 or 2)	1.57 (0.78-3.17)	0.21	0.77 (0.51-1.15)	0.20
LVI (Yes vs. no)	1.42 (0.87-2.32)	0.17	1.80 (1.36-2.39)	< 0.001
Chemotherapy (Neoadjuvant/adjuvant vs. no chemotherapy)	0.55 (0.30-1.04)	0.07	1.00 (0.62-1.61)	0.98
Radiotherapy (PMRT/WBRT/RNRT vs. no radiotherapy)	0.96 (0.50-1.85)	0.61	1.19 (0.80-1.77)	0.39
LN status (Positive vs. negative)	1.41 (0.86-2.31)	0.17	2.01 (1.48-2.72)	< 0.001

LVI: lymphovascular invasion; LN: lymph node; BCT: breast conserving therapy; PMRT: post-mastectomy radiotherapy; WBRT: whole breast radiotherapy; RNRT: regional nodal radiotherapy