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Basal Subtype of Invasive Breast Cancer is Associated with a Higher Risk of True Recurrence after Conventional Breast-Conserving Therapy

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Abstract

Purpose—To determine whether breast cancer subtype is associated with patterns of ipsilateral breast tumor recurrence (IBTR), either true recurrence (TR) or elsewhere local recurrence (ELR), among women with pT1-T2 invasive breast cancer (IBC) who receive breast-conserving therapy (BCT)

Methods and Materials—From 1/1998 to 12/2003, 1223 women with pT1-T2N0-3 IBC were treated with BCT (lumpectomy + whole breast radiation). Ninety percent of patients received adjuvant systemic therapy, but none received trastuzumab. Biologic subtype was approximated using estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2): luminal A (ER+ or PR+ and HER-2-), luminal B (ER+ or PR+ and HER-2+), HER-2 (ER- and PR- and HER-2+), and basal (ER- and PR- and HER-2-). Imaging, pathology and operative reports were reviewed by two physicians independently, including an attending breast radiologist. Readers were blinded to subtype and outcome. TR was defined as IBTR within the same quadrant and within three centimeters of the primary tumor. All others were ELR.

Results—At median follow-up of 70 months, 24 patients developed IBTR (5-year cumulative incidence 1.6%), including 15 TR and 9 ELR. At 5 years, basal (4.4%) and HER-2 (9%) subtypes

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None

had a significantly higher incidence of TR compared with luminal B (1.2%) and luminal A (0.2%) subtypes (p<0.0001). On multivariate analysis, basal subtype (HR 4.8, p=0.01), younger age at diagnosis (HR 0.97, p=0.05), and increasing tumor size (HR 2.1. p=0.04) were independent predictors of TR. Only younger age (HR 0.95, p=0.01) significantly predicted for ELR.

Conclusions—Basal and HER2 subtypes are significantly associated with higher rates of TR among women with pT1-T2 IBC after BCT. Younger age predicts for both TR and ELR. Strategies to reduce TR in basal breast cancers, such as increased boost doses, concomitant radiation and chemotherapy, or targeted therapy agents, should be explored.

Keywords

breast cancer; biologic subtype; basal; triple negative; local recurrence; true recurrence; elsewhere recurrence

Introduction

While breast-conserving therapy (BCT), consisting of conservative surgery followed by whole breast radiation, has become the standard of care for early-stage breast cancer, (1–3) ipsilateral breast tumor recurrence (IBTR) continues to be of clinical concern with an overall risk of 2–8% by 10 to 15 years in modern series (4–6). IBTR can occur as two different entities: true recurrence (TR) which is thought to arise in the vicinity of the original tumor from residual cancer cells, and elsewhere local recurrence (ELR) which is thought to occur as a *de novo* cancer or from previously undetected microscopic disease in a different area of the ipsilateral breast (7).

Clinical studies of conservative breast surgery alone report that 80–85% of IBTR occur in the vicinity of the original tumor (8, 9), and studies of IBTR after BCT report that 44–79% are TR (10–16). These findings have implications for treatment, as the rationale for considering accelerated partial breast irradiation (APBI) is based on the notion that most IBTR after BCT occur within the original tumor vicinity. Published consensus guidelines for APBI have attempted to identify those patients with a low risk of clinically-occult disease remote from the lumpectomy cavity who would be suitable for this treatment (17).

DNA microarray profiles can be used to classify breast tumors into distinct biologic subtypes (18, 19). Because this testing is often not feasible in the clinical setting, these subtypes can be approximated using commonly available markers of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) as follows: luminal A (ER+ or PR+ and HER-2-), luminal B (ER+ or PR+ and HER-2+), HER-2 (ER- and PR- and HER-2+), and basal (ER- and PR- and HER-2-) (20). Recent studies show that biologic subtypes are prognostic for local-regional recurrence and distant metastasis after BCT (21–25), with the basal and HER-2 subtypes associated with higher rates of both. In a subset analysis of the Danish post-mastectomy trials, these two subtypes were also associated with little to no benefit in overall survival after post-mastectomy radiation therapy (26).

The impact of biologic subtype on the pattern of IBTR in the breast is unclear. Further understanding of this relationship can help inform therapeutic decision-making, in particular with respect to the radiation field to the breast following conservative surgery. The purpose of this study was to determine whether breast cancer subtype, as approximated by ER, PR, and HER-2, is associated with the type of IBTR among women with early-stage breast cancer who receive BCT.

Methods and Materials

Patient selection

The study cohort included 1223 consecutively treated women with early stage invasive breast cancer who received breast conserving surgery followed by whole breast radiation from January 1, 1998 through December 31, 2003 at Dana-Farber Cancer Institute/Brigham and Women's Hospital (n=692) or Massachusetts General Hospital (n=531) in Boston, MA. All patients had newly diagnosed, nonmetastatic 2002 American Joint Committee on Cancer (AJCC) (27) pathologic stage T1-T2 invasive breast cancer. Patients with prior malignancy (except non-melanoma skin cancers), synchronous bilateral breast cancer, or treatment with preoperative systemic therapy were excluded. The study was approved by the Institutional Review Board of the affiliated hospitals.

Classification of subtype groups

Patients were categorized based on the receptor status of their primary tumor: luminal A (ER-positive or PR-positive and HER-2–negative), luminal B (ER-positive or PR-positive and HER-2–positive), HER-2 (ER-negative, PR-negative, and HER-2–positive), and basal (ER-negative, PR-negative, and HER-2–negative). ER and PR status were assessed by immunohistochemical (IHC) staining. Tumors were considered HER-2– positive if they were scored 3 on IHC staining or if they were scored 2 or greater by IHC staining and showed HER-2 amplification (ratio >2.0) based on fluorescence in situ hybridization (FISH). Tumors that scored 2 or greater by IHC staining in the absence of FISH amplification were considered HER-2 negative (28).

Treatment

All patients underwent local excision of the primary breast cancer and 1130 patients (92%) underwent surgical lymph node evaluation. Adjuvant chemotherapy was given to 46% of patients, hormonal therapy to 77% of patients, and both to 32% of patients. None of the patients received pre-operative chemotherapy, and none received adjuvant trastuzumab. All patients received external beam radiation therapy to the whole breast. Median dose was 60 Gy (range 20–72). The most common doses were 45 Gy in 1.8-Gy fractions to the whole breast followed by tumor-bed boost to 61 Gy, or 50 Gy in 2.0-Gy fractions to the whole breast followed by tumor-bed boost to 60 Gy. One patient chose to stop treatment after 20 Gy, despite counseling by the treating physician to complete the entire course of radiation. A separate supraclavicular or axillary field was typically added after axillary dissection only if there were four or more involved axillary lymph nodes.

Follow-Up

Patients were generally seen in follow-up 4 to 6 weeks after radiation therapy was completed, and then every 6 months thereafter with yearly breast imaging. For patients who discontinued follow-up, attempts were made to obtain follow-up information from their primary care physician. Follow-up time was counted from date of diagnosis to the date of the first event, or to the last known confirmed date of breast cancer disease-free status. In total, 64 patients (5%) were lost to follow-up.

Local recurrence and coding as true versus elsewhere

Patients from the cohort with IBTR as their first event were identified. All of these patients had yearly breast imaging and original images accessible. For each recurrence, imaging of the primary and recurrent tumor were reviewed with pathology reports to compare histology and operative notes to better characterize location of the recurrent tumor with respect to excision site and scars. Mammograms, magnetic resonance imaging (MRI), if available, and

ultrasounds were reviewed for each case by an attending breast radiologist (PF, DGS) and resident radiation oncologist (JAH). Each IBTR was coded as a TR if the recurrence was in the same quadrant of the breast and within three centimeters of the primary tumor bed. All other IBTR were coded ELR. Readers were blinded to biologic subtype.

Outcomes and statistical methods

The primary study endpoint was type of IBTR, either TR or ELR. Time to TR or ELR was a secondary endpoint. The primary study variable was biologic subtype. Additional covariates included age (continuous), grade (1 or 2 vs. 3), margin status (positive vs. <2mm but not on ink vs. ≥ 2mm), nodal status (positive vs. negative), tumor size (continuous), pathologic tumor stage (T, T1 vs. T2), and lymphovascular invasion (LVI present vs. absent or unknown).

Chi-square test was performed to compare baseline characteristics among the four subtype groups. A nonparametric K-sample test was used to compare medians across groups. The five-year actuarial estimates of TR and ELR were calculated by the Kaplan-Meier method and a log-rank test was used to compare incidence functions. Cox regression univariable analysis (UVA) was performed for TR and ELR. The association between subtype and time to TR or ELR as a first event was analyzed using Gray's competing risks multivariable analysis (MVA), and each significant factor on UVA was put into the model. Competing events included death and distant failure. All analyses were performed in Stata 11.1 (StataCorp, College Station, TX). All statistical tests were two-sided and statistical significance was defined as a p-value of 0.05.

Results

Baseline characteristics and association with biologic subtype

Patient characteristics of the cohort are shown in Table 1. The majority of patients (81%) had pT1 tumors and most (73%) were node negative. Margins were close (< 2 mm but not on ink) or negative (≥ 2 mm) in 96% of patients. The luminal A subtype made up 77% of the patient cohort and HER-2 only 4.3%. One patient received less than 50 Gy and did not have any disease recurrence.

As shown in Table 2, among the subtypes there were significant differences in median age ($p < 0.0001$), pT1 disease ($p<0.0001$), presence of LVI ($p=0.001$), node positivity ($p<0.0001$), and histologic grade ($p<0.0001$). HER-2 and basal subtypes were more frequently associated with younger age, more advanced pathologic T stage, lymph node involvement, higher grade, and LVI.

Rates of TR and ELR

At a median follow-up of 70.4 months, 24 patients developed IBTR as the site of first recurrence (5-year cumulative incidence = 1.6%). Of these, 15 (63%) were coded as TR and 9 (37%) were ELR. Mean time to TR was 3.6 years compared with 4.2 years to ELR which was not statistically significant ($p=0.5$).

Factors associated with TR

Table 3 summarizes results of the UVA of factors associated with TR. When compared with all other subtypes, basal subtype was associated with a seven-fold increased risk of TR ($p<0.0001$). Age at diagnosis was also associated with TR with a HR of 0.96 or a 4% decrease in risk per 1 year increase in age ($p=0.003$). Tumor size was associated with a two-and-a-half fold increase in TR per centimeter increase in size ($p=0.002$). Grade 3 disease and

node positivity were also associated with an increased risk of TR. Margin status and LVI were not significant on UVA.

Multivariable analysis (MVA) of factors associated with TR is shown in Table 4. Basal subtype remained significantly associated with increased risk of TR (HR 4.8, p=0.01). Younger age and larger tumor size also predicted for TR. Figure 1 shows the cumulative incidence plot of TR stratified by subtype. At 5 years, basal (4.4%) and HER-2 (9%) subtypes had a higher incidence of TR compared to luminal B (1.2%) and luminal A (0.2%) subtypes (p<0.0001).

Factors associated with ELR

On UVA, age at diagnosis was the only factor associated with ELR, with a HR of 0.95 (95% CI 0.91–0.98, p=0.01) or a 5% decrease in risk of ELR for every 1 year increase in age. Biologic subtype was not associated with ELR (p=0.59). The 5-year cumulative incidence of ELR was 0.48% (95% CI 0.2–1.2%).

Actuarial analysis of TR and ELR by age group

Table 5 shows five-year actuarial rates of TR and ELR by age group. Age cutpoints were chosen based on even distribution across quartiles, and by dividing the cohort by median age (55 years). The 5-year rate of TR was highest in patients less than 47 years of age (2.3%), with no events in patients older than 64. Similarly, rate of ELR was highest in patients less than 47 (1.6%), with no events in patients older than 55.

Discussion

We assessed whether biologic subtype, as approximated by ER, PR, and HER-2, is associated with the pattern of IBTR in women who underwent BCT for early-stage breast cancer. Basal subtype, when compared with all other subtypes, was an independent predictor of TR (HR 4.8, p=0.01). Younger age and increasing tumor size were also significantly associated with TR on MVA. Younger age was the only predictor of ELR, while subtype was not. Margin status was not a significant predictor of TR in the present study, but only 4% of patients had positive margins and all patients with IBTR had negative margins, thus limiting our ability to detect this association. We also found a high rate of TR among HER-2 subtype patients, although they made up only 4.3% of the cohort. The prevalence of HER-2 subtype patients in the Carolina Breast Cancer Study was only 6.7% so the small proportion of HER-2 patients appears similar to population-based studies (29).

The majority of IBTR in the present study were at or near the primary site (TR 63%) compared with 37% away from the primary site (ELR). These numbers are similar to those reported in other studies, with rates of TR generally ranging from 59–79% (4, 10–16). We also found the mean time to TR was 3.6 years compared with 4.2 years to ELR though the difference was not statistically significant. Longer time to ELR compared to TR is consistent with other studies (4, 11, 14–16, 30). In a study by Smith and colleagues of 130 patients with IBTR, 51% were considered new primary tumors compared with 44% TR (15). New primary tumors were distinctly different from the original primary with respect to location, histology or flow cytometry. This lower TR rate is likely because of the extended follow up period of 14.2 years over which time the number of TR levels off and ELR or “new primary” tumors increase.

There is no clear consensus on the ideal way to designate TR from ELR. Most studies take the location of the primary and recurrent tumor into account by quadrant when making this designation (4, 10, 11, 31). Komoike et al. used location and surgical margin to classify IBTR (13), Smith et al. also looked at change in histology and DNA flow cytometry (14),

while Huang et al. designated a TR as one located within 3 cm of the primary tumor bed and with the same histology (12). In a study by Recht et al. IBTR were classified as TR, marginal miss (MM), and ELR based on the location of the recurrence with respect to the radiation field and boost volume (15, 32). Kurtz et al. defined “new tumors” as occurring at least 5 cm away from the primary tumor (16). We designed our methodology after reviewing the studies above.

To our knowledge, the present study appears to be the only one to specifically look for association of different breast cancer subtypes with type of IBTR. Smith et al. reported that ER status was not related to location of IBTR, but their group did not specifically look at subtype (14). Huang et al. reported that more patients with ER+ tumors developed new primary tumors rather than TR (p=0.05) (12). This is similar to what we see in the present study where 6 of the 9 ELR were luminal A tumors. However, we have too few ELR events for this to establish statistical significance.

We found that basal subtype was associated with an increased risk of TR. Some studies have shown that the basal or triple negative subtype of breast cancer is associated with an increased risk of IBTR (22, 33), and a shorter median time to recurrence (31). Our results suggest that these recurrences are more often within or close to the primary tumor site. This finding is supported by evidence showing the biologic aggressiveness of basal or triple negative breast cancer (34, 35), and may even suggest some inherent resistance to radiation. There was also a high rate of TR among the HER-2 subtype patients in the current study. Voduc and colleagues determined molecular subtypes of 2,985 tumors, and found that the HER-2 and basal subtypes demonstrated an increased risk of regional recurrence after BCT (24). Another study found a higher rate of local-regional recurrence among ER/PR negative or HER-2 positive patients with T1a,b N0 breast cancer (21). In these studies, like the present study, none of the HER-2 positive patients received adjuvant trastuzumab.

The results of this study may have implications for the use of APBI. Had we found that a particular subtype predicted for ELR, this group could potentially be less suitable for APBI and possibly better treated with whole breast radiation. However, this was not the case in the present study. Given the small number of events and limited follow-up time, subtype was not associated with ELR. Also, the basal group had a higher rate of distant metastases (15.4% vs. 4.8% among all other subtypes, $p<0.0001$) and death (16.2% vs. 4.1% among all other subtypes, $p<0.0001$). Thus, in a competing risks analysis, more basal patients would have been censored prior to developing ELR. Longer follow up will be needed to better characterize the association of subtype and ELR. Nevertheless, evidence of the unsuitability of a specific subtype to APBI should come primarily from analyzing APBI trials and evaluating patterns of failures.

Younger age was associated with increased risk of ELR, which is consistent with findings reported by Komoike et al (13). However, Recht et al. showed that the incidence of TR/MM was higher in age ≤ 34 years compared with age > 34 years (17% vs. 8%), but there was little difference noted between rates of elsewhere recurrences (15). In our study, age was an independent risk factor for TR and ELR, particularly in women under 55 years of age. Young women with breast cancer are more likely than those with later-onset disease to carry a genetic predisposition to breast carcinoma, including mutations in BRCA1/BRCA2 tumor suppressor genes (36). Haffty et al. showed that carriers of BRCA1/BRCA2 mutations have significantly higher risks of late IBTR when compared with sporadic breast carcinoma patients (37). This may be consistent with the possible development of second primary tumors. Regardless of mediating factors, it is well reported in the literature that young age is an independent risk factor for local recurrence after BCT (38–41). The consensus statement from the American Society for Radiation Oncology (ASTRO) recommends against treating

women <50 years with APBI outside of a clinical trial, and few women in this age group have been treated with APBI in prospective studies (17). Our results support this recommendation.

The different patterns of recurrence among breast cancer subtypes could partially be explained by “early” versus “late” IBTR among the different subtypes. Luminal tumors tend to have a more indolent course (24), and it is possible that the rates of TR among the subtypes might equalize over time. Longer follow-up will be required to fully understand the pattern of IBTR among breast cancer subtypes over time.

There are several potential limitations to this study. Firstly, it is retrospective and may be subject to inherent biases. In addition, there were a limited number of events. Longer follow-up of this cohort will be needed to better characterize ELR or new primary tumors. Lack of adjuvant trastuzumab, which had not yet become the standard of care for patients with HER-2 positive early stage breast cancer (28, 42), tempers the findings for the luminal B and HER-2 groups. Subtypes were approximated with ER, PR, and HER-2 markers, rather than the gold standard of genotyping. However, given that receptor information is readily available in the clinic, this method may have more general applicability. Lastly, while our methodology for discerning TR from ELR was robust and consistently applied to each case, future research on quantitative DNA fingerprinting techniques may more objectively distinguish recurrent tumor from new primary breast cancer (43).

In conclusion, we found that basal subtype was a significant independent predictor of TR in women with T1-T2 breast cancer who receive BCT. Age was significantly associated with both TR and ELR. These results may have implications with respect to the radiation field, in particular whole breast compared with partial breast treatment. Nevertheless, further studies on the patterns of failure for patients treated with APBI with regard to biological subtypes are needed. Furthermore, future research towards reducing TR in basal or triple negative breast cancers, such as the use of targeted systemic agents, higher boost doses, or concomitant chemotherapy and radiation, is warranted.

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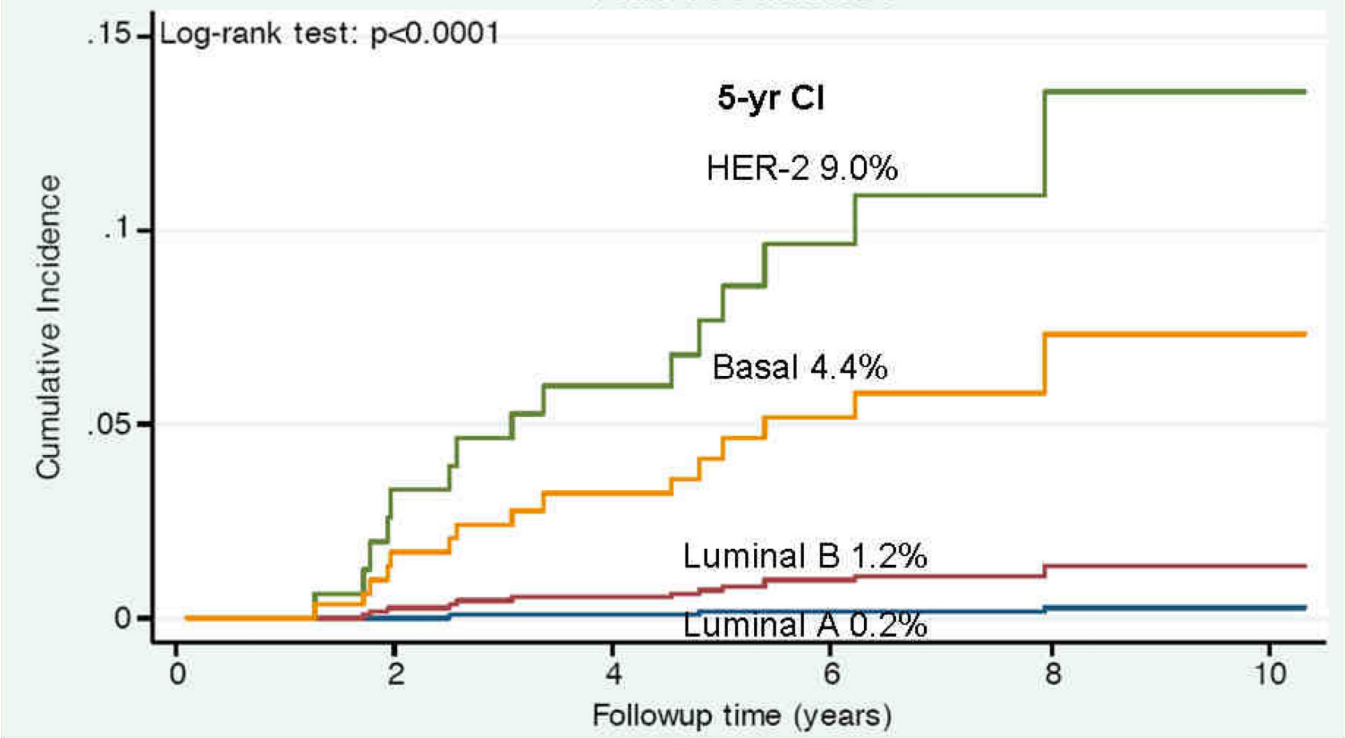

Figure 1.
Cumulative incidence plot of TR stratified by breast cancer subtype. Five-year rates of TR are shown, p<0.0001 (log-rank test).

Table 1

Baseline Patient Characteristics

	All patients (n=1223)	
Characteristic	**No.**	**%**
Age at diagnosis, median, years (range)	55 (23–89)	
Age, years		
<40	90	7.4
40–50	307	25.2
50–60	414	33.9
>60	408	33.5
Menopausal Status		
Pre	372	30.4
Post	742	60.6
Peri	102	8.3
Unknown	7	0.7
Pathologic T stage*		
T1mic	6	0.5
T1a	144	11.8
T1b	294	24.0
T1c	544	44.5
T2	235	19.2
Pathology		
Invasive ductal	958	78.3
Invasive lobular	138	11.3
Ductal + lobular	116	9.5
Tubular	5	0.4
Medullary	1	0.1
Mucinous	4	0.3
Unknown	1	0.1
Pathologic N stage†		
N0	888	72.6
N1	260	21.3
N2	51	4.2
N3	14	1.1
Nx	8	0.7
Grade		
1	311	25.4
2	509	41.6

	All patients (n=1223)	
Characteristic	**No.**	**%**
3	386	31.6
Unknown	17	1.4
Margins		
Negative (≥ 2mm)	1013	82.8
Close (< 2mm but not on ink)	160	13.2
Positive (on ink)	48	3.9
Unknown	1	0.1
LVI positive	318	26
LVI negative	900	73.6
Unknown	4	0.3
Subtype		
Luminal A	937	76.6
Luminal B	98	8.0
Her 2	52	4.3
Basal	136	11.1
RT dose		
< 50 Gy	1	0.1
50– 60 Gy	710	57.8
> 60 Gy	517	42.1
Chemotherapy		
Yes	558	45.7
No	663	54.3
Unknown	0	0
Hormonal Therapy		
Yes	942	77.1
No	277	22.7
Unknown	2	0.2

*† Pathologic T and N stage are based on AJCC 2002 6th edition guidelines (27)

LVI=lymphovascular invasion

RT=radiation therapy

Gy= Gray

Table 2

Baseline Patient Characteristics Stratified by Subtype

Characteristic	All pts (n=1223)	Luminal A (n=937)	Luminal B (n=98)	Her-2 (n=52)	Basal (n=136)	p-value
Median age (years)	55	56	54	50	53	<0.0001
T1 (%)	80	84	76	67	64	<0.0001
LVI (%)	26	24	40	39	27	0.001
Node positive (%)	27	24	36	46	32	<0.0001
Grade 3 (%)	32	20	47	71	84	<0.0001
Systemic treatment, (%)	90	93	92	73	80	<0.0001
Chemotherapy	46	38	67	69	76	<0.0001
Hormonal therapy	77	89	90	10	10	<0.0001
Margins positive, %	4	4	6	2	4	NS
Median RT Dose, Gy	60	60	60	60	61	NS
Post-menopausal, %	60	62	55	46	58	NS

LVI=lymphovascular invasion

RT=radiation therapy

Gy= Gray

Table 3

Univariable Analysis of factors associated with TR

Characteristic	HR	95% CI	p-value
Basal vs. all other subtypes	7.2	2.6–19.7	p<0.0001
Age at diagnosis, years (continuous)	0.96	0.93–0.99	p=0.003
Tumor size, cm (continuous)	2.5	1.4–4.5	p=0.002
Grade 3 vs. Grade 1/2	14.7	3.3–64.3	p<0.0001
Node positive vs. negative	4.1	1.5–11.7	p=0.008

HR= hazard ratio

CI=confidence interval

cm=centimeter

Table 4

Multivariable Analysis of Factors Associated with TR

Characteristic	HR	95% CI	p-value
Basal subtype	4.8	1.4–15.8	p=0.01
Age at diagnosis, years (continuous)	0.97	0.94–0.99	p=0.05
Tumor size, cm (continuous)	2.1	1.1–4.2	p=0.04

HR= hazard ratio

CI=confidence interval

cm=centimeter

Table 5

Five-year Rates of TR and ELR by Age Groups *

Age (years)	5 year rates of TR or ELR, % (95% CI)	
	TR	ELR
< 47	2.3 (1.1 – 5.2)	1.6 (0.6 – 4.2)
47–55	1.2 (0.4 – 3.8)	0.3 (0.05– 2.4)
55–64	1.0 (0.3 – 3.2)	0
> 64	0	0
< 55	1.8 (0.9 – 3.5)	1.0 (0.4 – 2.3)
> 55	0.5 (0.2 – 1.6)	0

* Cutpoints were chosen based on even distribution across quartiles, and divided by median age (55 years)

CI=confidence interval