Local–regional recurrence in women with small node-negative, HER2-positive breast cancer: results from a prospective multi-institutional study (the APT trial)

Jennifer R. Bellon[1] · Hao Guo[2] · William T. Barry[2] · Chau T. Dang[3] · Denise A. Yardley[4] · Beverly Moy[5] · P. Kelly Marcom[6] · Kathy S. Albain[7] · Hope S. Rugo[8] · Matthew Ellis[9] · Antonio C. Wolff[10] · Lisa A. Carey[11] · Beth A. Overmoyer[12] · Ann H. Partridge[12] · Clifford A. Hudis[3,13] · Ian Krop[12] · Harold J. Burstein[12] · Eric P. Winer[12] · Sara M. Tolaney[12]

Received: 26 March 2019 / Accepted: 12 April 2019 / Published online: 19 April 2019

Abstract

Purpose Women with HER2-positive breast cancer treated prior to effective anti-HER2 therapy have higher rates of local–regional recurrence (LRR) than those with HER2-negative disease. Effective systemic therapy, however, has been shown to decrease LRR. This study examines LRR in women with HER2-positive breast cancer treated on a single-arm prospective multicenter trial of adjuvant trastuzumab (H) and paclitaxel (T).

Methods Patients with HER2-positive tumors ≤ 3.0 cm with negative axillary nodes or micrometastatic disease were eligible. Systemic therapy included weekly T and H for 12 weeks followed by continuation of H to complete 1 year. Radiation therapy (RT) was required following breast-conserving surgery (BCS), but dose and fields were not specified. Disease-free survival (DFS) and LRR-free survival were calculated using the Kaplan–Meier method.

Results Of the 410 patients enrolled from September 2007 to September 2010, 406 initiated protocol therapy and formed the basis of this analysis. A total of 272 (67%) had hormone receptor-positive tumors. Of 162 patients undergoing mastectomy, local therapy records were unavailable for two. None of the 160 for whom records were available received RT. Among 244 BCS patients, detailed RT records were available for 217 (89%). With a median follow-up of 6.5 years, 7-year DFS was 93.3% (95% CI 90.4–96.2), and LRR-free survival was 98.6% (95% CI 97.4–99.8).

Conclusion LRR in this select group of early-stage patients with HER2-positive disease receiving effective anti-HER2 therapy is extremely low. If confirmed in additional studies, future investigational efforts should focus on de-escalating local therapy.

Keywords HER2 · Stage I · Local regional recurrence · Breast cancer

Introduction

While breast cancer molecular subtype has long been known to impact the risk of distant disease recurrence [1], the relationship between subtype and risk of local regional recurrence (LRR) has only been more recently appreciated. Multiple large retrospective series in the last decade have shown a lower risk of LRR in women with estrogen receptor-positive and progesterone receptor-positive tumors who are also low and intermediate grade (luminal A approximation), and higher rates of LRR in patients with both hormone receptor and HER2-negative tumors, as well as those with HER2-positive tumors [2–4]. However, many of these studies included patients treated prior to the routine use of anti-HER2 therapy. More recently, the beneficial effects of effective systemic therapy on the risk of LRR have been well documented [5] and is likely the largest factor contributing to the lower risk of LRR seen in modern series. Moreover, this effect has been seen both with endocrine therapy and conventional chemotherapy, as well as with targeted agents [5–8]. In light of the benefits of systemic therapy on LRR rates, this study examines the risk of LRR in a uniform group of women with low-risk, HER2-positive disease,

✉ Jennifer R. Bellon
Jennifer_bellon@dfci.harvard.edu

Extended author information available on the last page of the article

receiving anti-HER2-based chemotherapy on a prospective single-arm trial.

Methods

Eligible patients included those with HER2-positive tumors (defined as 3+ staining on immunohistochemistry analysis and/or fluorescence in situ hybridization ratio of HER2 to chromosome 17 centromere greater than or equal to 2) smaller than or equal to 3.0 cm. Patients were required to have a sentinel node biopsy or axillary dissection. If there was micrometastatic (< 0.2 mm) disease in the sentinel node, then a completion dissection without further nodal involvement was required. Patients with macrometastatic disease in either the sentinel node or axillary dissection were excluded.

Systemic therapy consisted of weekly paclitaxel (T; 80 mg/m^2) and trastuzumab (H; 4 mg/kg week 1 followed by 2 mg/kg for each subsequent week) for 12 weeks. H was continued either weekly (2 mg/kg) or every 3 weeks (6 mg/kg) to complete 1 year. Adjuvant endocrine therapy in patients with estrogen and/or progesterone receptor-positive tumors was encouraged, although choice of endocrine agent was left to the treating physician's discretion.

Radiation therapy (RT) was mandated following breast-conserving surgery (BCS), although the doses, target volumes, and techniques were not specified. Radiation records were not collected as part of the core study materials. However, radiation completion notes were obtained following study accrual whenever possible. LRR was defined as recurrence in the ipsilateral breast or chest wall following breast-conserving surgery or mastectomy, respectively, and in the ipsilateral infraclavicular, supraclavicular, axillary or internal mammary lymph node regions following either surgery.

Primary endpoint of the main study was invasive disease-free survival (DFS). The null hypothesis was a 3-year event rate of 9.2%, and the alternate hypothesis, a 3-year event rate of 5% or less. This resulted in 96% probability of rejecting the null hypothesis. DFS and LRR-free survival were calculated using the Kaplan–Meier method. The present sub-study was designed to retrospectively analyze the risk of local recurrence in this uniformly treated population of women with HER2-positive disease receiving anti-HER2 therapy.

Results

Patient and tumor characteristics were reported previously (Table 1) [9]. Patients were accrued between September 2007 and September 2010. Four hundred and six patients initiated protocol therapy and form the basis of this analysis. Only 36 patients (9%) had T2 (> 2.0 cm and ≤ 3.0 cm) primary tumors; the remaining patients had tumors 2.0 cm or smaller. Overall, 272 (67%) patients had estrogen and/or progesterone receptor-positive tumors. Most were node negative, although 6 patients (1%) had micrometastatic (2 mm or smaller) nodal disease.

One hundred sixty-two patients underwent mastectomy. None of the 160 (99% of the entire mastectomy cohort) for whom documentation was available received post-mastectomy radiation therapy. Two hundred forty-four patients

Table 1 Patient and treatment characteristics [9]

Characteristic	All treated patients ($n = 406$) *N* (%)
Age group (years)	
< 50	132 (33)
50–59	137 (34)
60–69	96 (24)
≥ 70	41 (10)
Sex	
Female	405 (100)
Male	1 (< 1)
Race	
White	351 (86)
Black or African American	28 (7)
Asian	11 (3)
Other	16 (4)
Size of primary tumor	
T1mi (≤ 0.1 cm)	9 (2)
T1a (0.1–≤ 0.5 cm)	68 (17)
T1b (> 0.5–≤ 1.0 cm)	124 (31)
T1c (> 1.0–≤ 2.0 cm)	169 (42)
T2 (> 2.0–≤ 3.0 cm)	36 (9)
Histologic grade	
I—Well differentiated	44 (11)
II—Moderately differentiated	131 (32)
III—Poorly differentiated	228 (56)
Unknown	3 (1)
ER status	
Positive	260 (64)
Negative	141 (35)
Borderline	5 (1)
PR status	
Positive	201 (50)
Negative	196 (48)
Borderline	8 (2)
Unknown	1 (< 1)
HR status	
Positive	272 (67)
Negative	134 (33)

underwent BCS. Radiation records were available for 217 of these patients (89%). Nine of these patients (4%) were treated with accelerated partial breast irradiation. Two hundred and eight patients (96%) received radiation to the whole breast, and of these, 202 (97%) had additional boost radiation to the lumpectomy site. Among those who received whole breast radiation, 89% had conventional fractionation, and 11% hypofractionation (fraction size greater than 2.5 Gy). No patient had a separate nodal field.

The current analysis includes follow-up through November 2016 with 2390 patient years of follow-up, and a median follow-up of 6.5 years. LRR-free survival at 7 years was 98.6% (95% CI 97.4–99.8%); 99.0% (95% CI 97.7–100%) among BCS patients and 98.0% (95% CI 95.8–100%) among mastectomy patients (Fig. 1). Seven-year DFS was 93.3% (95% CI 90.4–96.2%); 92.1% (95% CI 88.0–96.3%) among BCS patients and 95.2% (95% CI 91.8–98.8%) among mastectomy patients (Fig. 2).

Five patients experienced LRR as a first site of recurrence (3 following mastectomy, and 2 following BCS). All 3 local recurrences following mastectomy were in the ipsilateral axilla. All had undergone a negative sentinel node biopsy (2 patients had 0/3 sentinel nodes, 1 patient had 0/1 sentinel nodes). One of the patients with an axillary recurrence had hormone receptor-negative disease, the other 2 had hormone receptor-positive tumors. Two patients following BCS had recurrences in the ipsilateral breast. One had been treated with conventional fractionation to the whole breast (46.0 Gy in 23 fractions) followed by a 14.0 Gy lumpectomy site cone-down in 7 fractions. The other patient who experienced an ipsilateral breast recurrence had received hypofractionation to both the breast and the lumpectomy site cone down (42.72 Gy in 16 fractions whole breast followed by 9.0 Gy in 3 fractions to the lumpectomy site). Both patients who had ipsilateral breast recurrences had hormone receptor-positive tumors.

Discussion

While the multiple subtypes of breast cancer, and their attendant impact on distant disease recurrence has long been appreciated [1], it is only in the last 10–15 years that the impact of subtype on LRR has also been described. Multiple groups have demonstrated higher rates of LRR among women with triple-negative disease (estrogen and progesterone receptor-negative, HER2-negative), and HER2-positive tumors, than those with hormone receptor-positive, HER2-negative tumors [2–4]. For example, Nguyen et al. [2] in a retrospective review of 793 consecutive patients treated with breast conservation between 1998 and 2001 found cumulative incidence of local recurrence of 0.8% for patients with luminal A approximated tumors (defined as estrogen receptor or progesterone receptor-positive, HER2-negative; 95% CI 0.3–2.2) compared to 8.4% for HER2 tumors (defined as estrogen receptor-negative, progesterone receptor-negative, and HER2-positive; 95% CI 2.2–30), and 7.1% for patients with triple-negative tumors (95% CI 3.0–16). However, these studies were largely in the era prior to effective anti-HER2 therapy. More recent studies have demonstrated low rates of LRR among women receiving anti-HER2 treatment. In a review of patients treated within the National Comprehensive Cancer Network (NCCN), Tseng et al. [10] found a cumulative incidence of isolated LRR of only 0.26% (95% CI 0.01–0.88%) for patients with HER2-positive disease treated with trastuzumab with a median follow-up of 50.1 months. Similarly, in the combined National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and the North Central Cancer Treatment Group N9831 studying trastuzumab concurrent and following paclitaxel (T) after doxorubicin and cyclophosphamide (AC) compared with ACT alone, LRR as a first event was decreased in patients with HER2-positive disease receiving trastuzumab [8]. Fifty-seven patients had an isolated LRR in the control arm compared with 27 among those randomized to a trastuzumab-containing regimen. A meta-analysis of 6 randomized trials [11] also showed a reduction in the risk of LRR with the addition of trastuzumab (OR 0.53, 95% CI 0.44–0.65, $p < 0.001$).

The reduction in LRR with anti-HER2 therapy mimics a general trend of improvements in LRR with the addition of systemic therapy. This seems to hold true with hormonal therapy as well as chemotherapy [5, 7] and with increasingly effective chemotherapy [6]. In the present study, which benefitted from a uniform patient population and systemic therapy regimen, the risk of LRR was exceptionally low, despite including patients with T2 (≤ 3 cm) and estrogen receptor-negative tumors. LRR at 7 years was 99.0% (95% CI 97.7–100%) among BCT patients and 98% (95% CI 95.8–100%) among mastectomy patients.

This review is limited by its retrospective nature. While the systemic therapy was a specified component of the prospective protocol, local management, including type of surgery, as well as radiation fields, doses and technique were at the discretion of the treating physician. In addition, the focus on low-risk patients and resultant low rate of LRR did not permit identification of risk factors for recurrence that might guide further trials.

Future directions include prospective investigation of omitting radiation in women with early-stage disease undergoing breast conservation. Omission of radiation has been previously studied in women with small, node-negative cancers, and in fairly unselected women, has typically shown higher rates of in-breast recurrence. One representative study from Princess Margaret Hospital randomized 769 women to tamoxifen alone or tamoxifen with radiation [12].

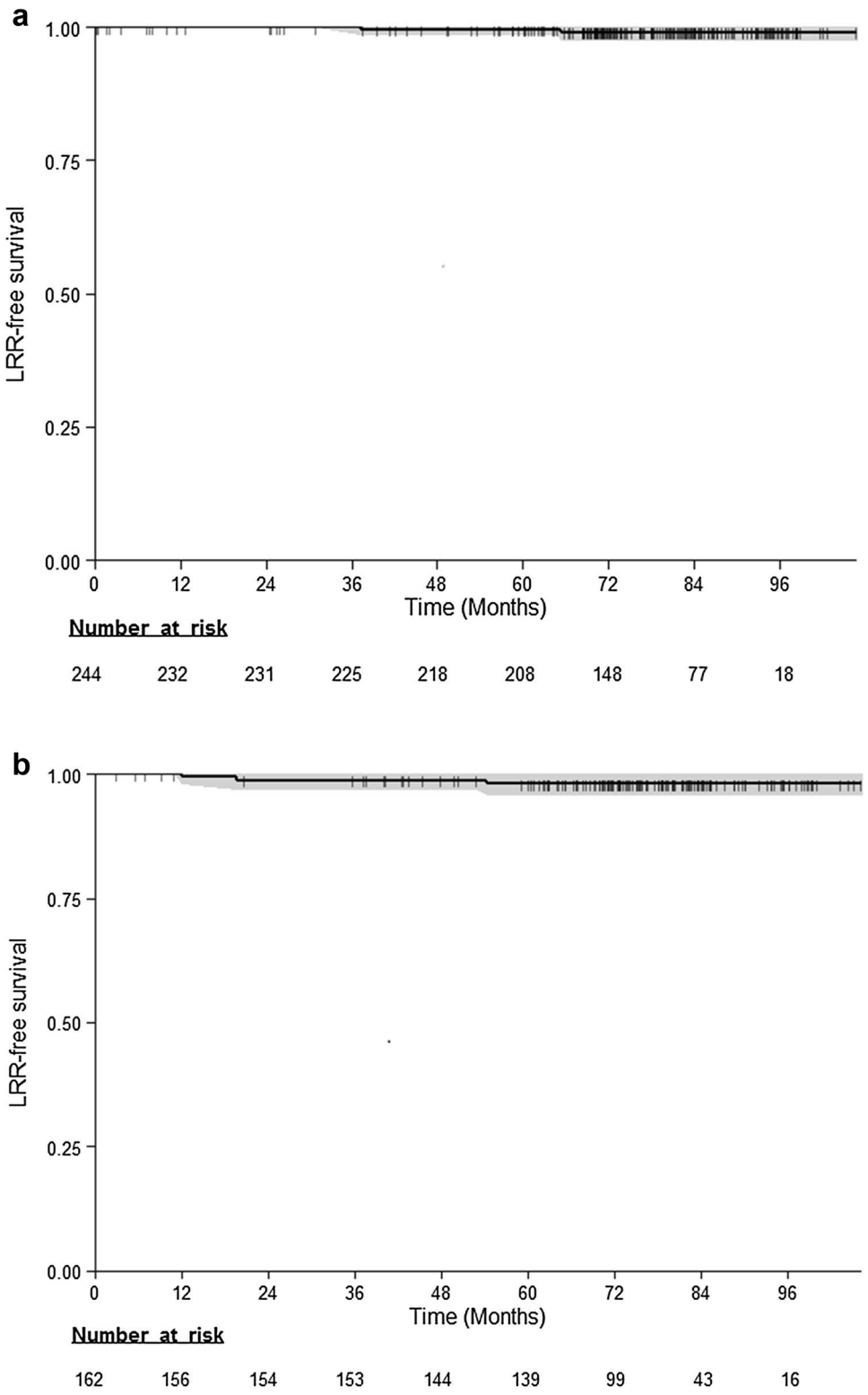

Fig. 1 **a** Local–regional recurrence-free survival among breast conservation patients. **b** Local–regional recurrence-free survival among mastectomy patients

At 5.6 years, local recurrence was 7.7% in the tamoxifen alone group, and 0.6% in the women receiving tamoxifen and radiation (hazard ratio 8.3; 95% CI 3.3–21.2, $p < 0.001$). However, when the authors retrospectively looked back at a subset of women for whom immunohistochemical biomarkers permitted an approximation of intrinsic subtype, the benefit of radiation in women with luminal A approximation was numerically modest and not statistically significant (3.3% vs. 7.3% at 10 years, $p = 0.11$) [13]. Several studies are currently enrolling patients with

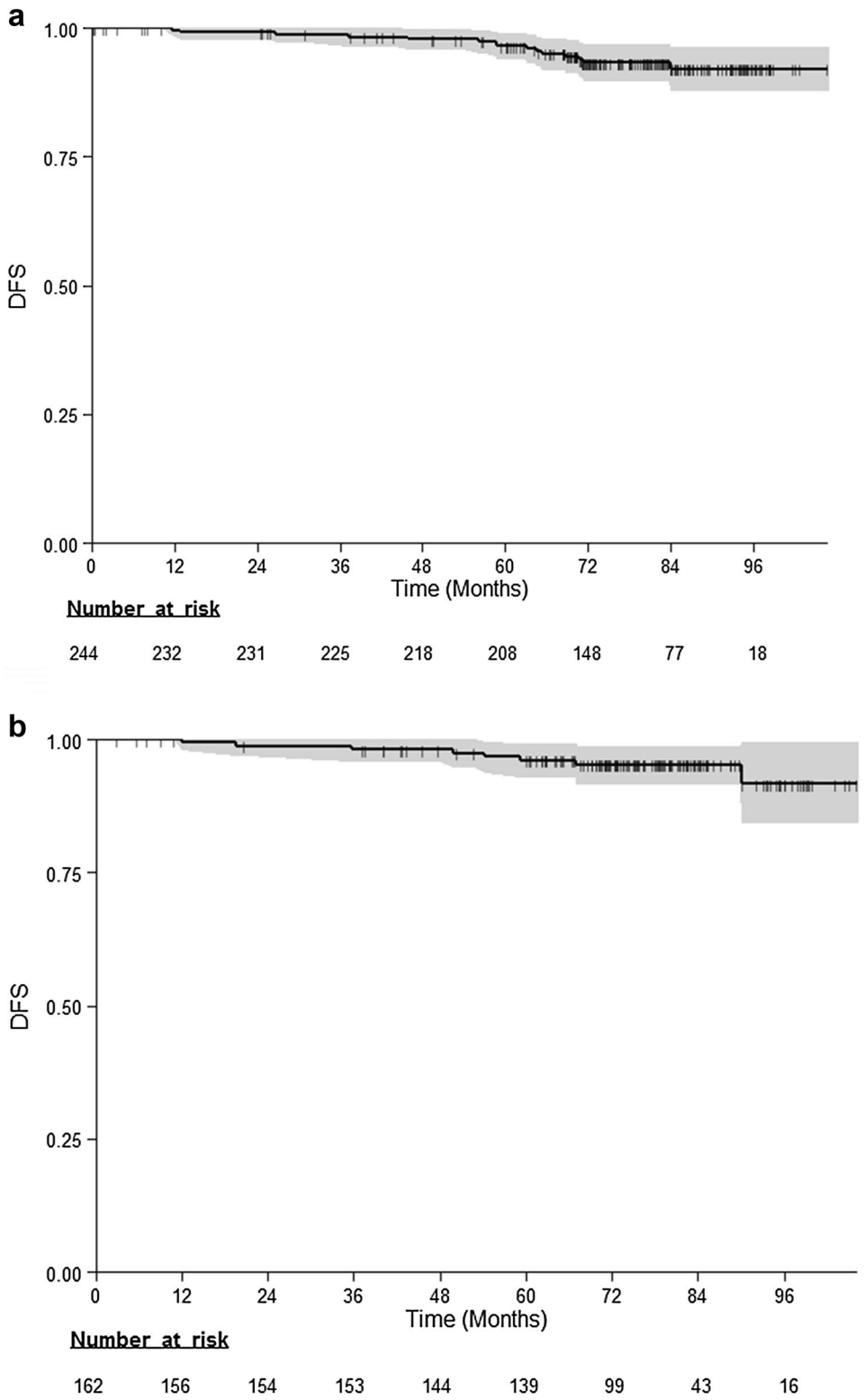

Fig. 2 **a** Disease-free survival among breast-conservation patients. **b** Disease-free survival among mastectomy patients

putative low-risk estrogen receptor-positive, HER2-negative tumors in prospective trials utilizing hormonal therapy in lieu of adjuvant radiation following breast-conservation. Low-risk patients are identified by either PAM50 (PRECISION, NCT02653755; EXPERT, NCT02889874), OncotypeDX (IDEA, NCT02400190) or Ki67 (LUMINA, NCT01791829). Similarly, early-stage patients receiving effective anti-HER2 therapy may also be appropriate for protocol-based study of the omission of radiation, due to their low rate of local recurrence with radiation. Despite

recent efforts to improve the safety of radiation therapy, it is inconvenient, and associated with both acute and chronic moribidity, as well as a small risk of second malignancy. Identifying women in whom radiation therapy can safely be omitted is an important effort in improving quality of life and decreasing treatment-related complications. While hormone receptor-positive, HER2-positive patients are particularly attractive candidates for such an approach, as they are also appropriate recipients of hormonal therapy, the present study showed equally low rates of LRR in both hormone receptor-positive and hormone receptor-negative tumors, suggesting that perhaps small anatomic size alone may be an adequate selection factor in this population.

Other opportunities for investigation include omission of nodal radiation in patients with HER2-positive tumors and involved axillary lymph nodes following BCS, and similarly omission of post-mastectomy radiation therapy in women with HER2-positive disease and 1–3 axillary nodes. In the era prior to HER2-directed therapy, the risk of regional recurrences and recurrences following mastectomy were higher in women with HER2-positive disease. Voduc et al. [4] retrospectively studied the impact of approximated biologic subtype in 2985 patients with non-metastatic breast cancer undergoing primary breast surgery in the era prior to anti-HER2 therapy. In the breast conservation cohort, 10-year risk of regional recurrence was 3% among patients with luminal A tumors compared to 16% in those with HER2-enriched disease. Similarly, the risk of both chest wall and regional nodal recurrences was elevated in mastectomy patients with HER-enriched tumors compared to those with luminal A disease. Moreover, randomized trials have shown a DFS benefit to supraclavicular and internal mammary radiation in women with node-positive and high-risk node-negative disease. These studies, however, predated the routine use of anti-HER2 therapy [14, 15]. Although only a minority of the patients on the present study had involved axillary nodes (micrometastasis only), the very low rate of LRR suggests that that omission of nodal RT in the BCS setting, and omission of RT altogether following mastectomy in women with limited nodal involvement, may be reasonable avenues for further study.

Prior to effective systemic therapy, potential improvements in survival with aggressive local therapy were largely overshadowed by distant metastases. This was likely the case in the landmark NSABP B-04 study [16], where there was no difference in survival between patients randomized to radical mastectomy, total mastectomy with adjuvant radiation, and total mastectomy with neither dissection nor axillary radiation. Distant DFS was low in both groups (38–46% at 25 years, without differences between the arms). However, as the ability to control microscopic metastases increased with gains in systemic therapy, improvements in local control translated into decreases in distant metastases and better overall survival [17]. This was seen in both the Danish post-mastectomy trials (82b and 82c) [18, 19]. It is conceivable that in very select patients with HER2-positive breast cancer, systemic therapy is now sufficient treatment for both local as well as distant disease, potentially permitting safe de-escalation of local therapy [20] and should be investigated in future studies.

Funding Genentech provided funding for the conduct of this trial.

Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest JB receives honorarium from UpToDate, Wolters Kluwer, The International Journal of Radiation Oncology, Biology and Physics, Leidos Pharmaceuticals, Accuray, and research funding from Prosigna. WTB reports research funding (institution) from Pfizer. CTD has received institutional research funding from and has served as advisor/consultant for Roche/Genentech, PUMA, Pfizer, Amgen, GlaxoSmithKline; in last 2 years CTD has received institutional research funding from Roche/Genentech and PUMA. BM receives institutional research funding from Puma Biotechnology. KSA has received one-time advisory board honoraria (with travel reimbursements) from Genentech/Roche, Genomic Health Inc, Novartis, Pfizer and Myriad and from Puma (as chair of an IDMC). ACW receives institutional research funding from Biomarin, Celldex, and Pfizer.BAO receives institutional research funding from Eisai, Incyte. IEK receives institutional research funding from Genentech/Roche and Pfizer and served as an advisor/consultant and received honoraria from Genentech/Roche, Daiichi/Sankyo, Macrogenomics, Context Therapeutics, Seattle Genetics and Taiho Oncology. EPW has served as an advisor to Genentech/Roche, Eli Lilly, and GSK, and serves on the Scientific Advisory Board for Leap Therapeutics. SMT receives institutional research funding from Novartis, Genentech, Eli Lilly, Pfizer, Merck, Exelixis, Eisai, Bristol Meyers Squibb, AstraZeneca, Cyclacel, Immunomedics, Odenate, and Nektar. SMT has served as an advisor/consultant to Novartis, Eli Lilly, Pfizer, Merck, AstraZeneca, Eisai, Puma, Genentech, Immunomedics, Nektar, Tesaro, Bristol Meyers Squibb, and Nanostring.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, Demeter J, Perou CM, Lonning PE, Brown PO, Borresen-Dale AL, Botstein D (2003) Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 100(14):8418–8423. https://doi.org/10.1073/pnas.0932692100
2. Nguyen PL, Taghian AG, Katz MS, Niemierko A, Abi Raad RF, Boon WL, Bellon JR, Wong JS, Smith BL, Harris JR (2008)

Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 26(14):2373–2378. https://doi.org/10.1200/JCO.2007.14.4287
3. Millar EK, Graham PH, O'Toole SA, McNeil CM, Browne L, Morey AL, Eggleton S, Beretov J, Theocharous C, Capp A, Nasser E, Kearsley JH, Delaney G, Papadatos G, Fox C, Sutherland RL (2009) Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. J Clin Oncol 27(28):4701–4708. https://doi.org/10.1200/JCO.2008.21.7075
4. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H (2010) Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 28(10):1684–1691. https://doi.org/10.1200/JCO.2009.24.9284
5. Early Breast Cancer Trialists' Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365(9472):1687–1717. https://doi.org/10.1016/S0140-6736(05)66544-0
6. Sartor CI, Peterson BL, Woolf S, Fitzgerald TJ, Laurie F, Turrisi AJ, Bogart J, Henderson IC, Norton L (2005) Effect of addition of adjuvant paclitaxel on radiotherapy delivery and locoregional control of node-positive breast cancer: cancer and leukemia group B 9344. J Clin Oncol 23(1):30–40. https://doi.org/10.1200/JCO.2005.12.044
7. Anderson SJ, Wapnir I, Dignam JJ, Fisher B, Mamounas EP, Jeong JH, Geyer CE Jr, Wickerham DL, Costantino JP, Wolmark N (2009) Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. J Clin Oncol 27(15):2466–2473. https://doi.org/10.1200/JCO.2008.19.8424
8. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353(16):1673–1684. https://doi.org/10.1056/NEJMoa052122
9. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo HS, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA, Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP (2015) Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 372(2):134–141. https://doi.org/10.1056/NEJMoa1406281
10. Tseng YD, Uno H, Hughes ME, Niland JC, Wong YN, Theriault R, Blitzblau RC, Moy B, Breslin T, Edge SB, Hassett MJ, Punglia RS (2015) Biological subtype predicts risk of locoregional recurrence after mastectomy and impact of postmastectomy radiation in a large national database. Int J Radiat Oncol Biol Phys 93(3):622–630. https://doi.org/10.1016/j.ijrobp.2015.07.006
11. Yin W, Jiang Y, Shen Z, Shao Z, Lu J (2011) Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. PLoS ONE 6(6):e21030. https://doi.org/10.1371/journal.pone.0021030
12. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, Weir LM, Olivotto IA (2004) Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 351(10):963–970. https://doi.org/10.1056/NEJMoa040595
13. Liu FF, Shi W, Done SJ, Miller N, Pintilie M, Voduc D, Nielsen TO, Nofech-Mozes S, Chang MC, Whelan TJ, Weir LM, Olivotto IA, McCready DR, Fyles AW (2015) Identification of a low-risk luminal a breast cancer cohort that may not benefit from breast radiotherapy. J Clin Oncol 33(18):2035–2040. https://doi.org/10.1200/JCO.2014.57.7999
14. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN, Investigators MAS (2015) Regional nodal irradiation in early-stage breast cancer. N Engl J Med 373(4):307–316. https://doi.org/10.1056/NEJMoa1415340
15. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M, De Winter K, Marnitz S, Barillot I, Scandolaro L, Vonk E, Rodenhuis C, Marsiglia H, Weidner N, van Tienhoven G, Glanzmann C, Kuten A, Arriagada R, Bartelink H, Van den Bogaert W, Oncology ER, Breast Cancer G (2015) Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 373(4):317–327. https://doi.org/10.1056/NEJMoa1415369
16. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N (2002) Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 347(8):567–575. https://doi.org/10.1056/NEJMoa020128
17. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366(9503):2087–2106. https://doi.org/10.1016/S0140-6736(05)67887-7
18. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB, Blichert-Toft M, Mouridsen HT (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 353(9165):1641–1648. https://doi.org/10.1016/S0140-6736(98)09201-0
19. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 337(14):949–955. https://doi.org/10.1056/NEJM199710023371401
20. Punglia RS, Morrow M, Winer EP, Harris JR (2007) Local therapy and survival in breast cancer. N Engl J Med 356(23):2399–2405. https://doi.org/10.1056/NEJMra065241

Affiliations

Jennifer R. Bellon[1] · Hao Guo[2] · William T. Barry[2] · Chau T. Dang[3] · Denise A. Yardley[4] · Beverly Moy[5] · P. Kelly Marcom[6] · Kathy S. Albain[7] · Hope S. Rugo[8] · Matthew Ellis[9] · Antonio C. Wolff[10] · Lisa A. Carey[11] · Beth A. Overmoyer[12] · Ann H. Partridge[12] · Clifford A. Hudis[3,13] · Ian Krop[12] · Harold J. Burstein[12] · Eric P. Winer[12] · Sara M. Tolaney[12]

1 Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, 450 Brookline Avenue, Boston, MA, USA

2 Department of Statistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA

3 Breast Cancer Medicine Service, Solid Tumor Division, Department of Medicine, Memorial Sloan Kettering Cancer Center and Department of Medicine, Weill Cornell Medical Center, New York, NY, USA

4 Department of Medical Oncology, Sarah Cannon Cancer Center, Nashville, TN, USA

5 Department of Hematology–Oncology, Massachusetts General Hospital, Boston, MA, USA

6 Division of Medical Oncology, Department of Medicine, Duke Cancer Institute, Durham, NC, USA

7 Division of Hematology/Oncology, Department of Medicine, Cardinal Bernardin Cancer Center, Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA

8 Department of Medicine, Division of Oncology, Helen Diller Comprehensive Cancer Center, University of California, San Francisco, CA, USA

9 Department of Medical Oncology, Baylor Clinic-Lester and Sue Smith Breast Center, Houston, TX, USA

10 Department of Oncology, Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA

11 Department of Medical Oncology, UNC Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA

12 Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

13 Present Address: American Society of Clinical Oncology, Alexandria, VA, USA