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EPIDEMIOLOGY

Trends in utilization of hypofractionated whole breast irradiation (HF-WBI) in triple negative breast cancer (TNBC): a national cancer database (NCDB) analysis

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Abstract

Purpose We sought to identify trends over time with respect to the use of hypofractionated whole breast irradiation (HF-WBI) in women with triple negative breast cancer (TNBC) in the national cancer database (NCDB).

Methods Trends in utilization of HF-WBI in women diagnosed with T1-2N0 TNBC in the NCDB between 2008 and 2013 were analyzed. Case-matched luminal A women were used for comparison. Variables included age, race, year of diagnosis, insurance status, income quartile, receipt of neoadjuvant chemotherapy, and institution (academic vs. community). Chi square, logistic regression, and multivariate analysis was performed.

Results Utilization of HF-WBI among the 53,269 TNBC women identified steadily increased from 4.7% in 2008 to 14.0% in 2013 for women with TNBC compared to luminal A cancer whose utilization increased from 7.3 to 23.3% over the same time frame ($p < 0.001$). On univariate analysis, HF-WBI was associated with increasing age ($p < 0.001$), Medicare insurance ($p < 0.001$), race ($p = 0.041$), diagnosis after 2011 ($p < 0.001$), higher income quartile ($p < 0.001$), and treatment at academic institutions ($p < 0.001$). On multivariate analysis, age ($p < 0.001$, OR 1.038 per year), income quartile ($p = 0.002$, OR 1.061 per increase in quartile), treatment at an academic institution ($p < 0.001$, OR 1.78) significantly increased use of HF-WBI.

Conclusions Treatment at an academic center and year of diagnosis were most correlated with increased HF-WBI in T1-2N0 TNBC women in the NCDB from 2008 to 2013, followed by increasing age and income. Only 14% of T1-2N0 TNBC women received HF-WBI in 2013. Focus on increased utilization is needed for non-academic centers, lower income, and younger women.

Keywords Triple negative · Hypofractionated · Early stage · Breast cancer

Introduction

Breast cancer remains the most commonly diagnosed cancer among women, with an incidence of 268,670 breast cancer diagnoses in 2018 in the United States [1]. Triple negative breast cancer (TNBC) comprises a subset of breast cancer patients whose tumors do not express estrogen or progesterone receptor positivity, and lack Her2/neu amplification. This subset of breast cancer accounts for approximately 12–17% of all breast cancers in the United States, and biologically behaves more aggressively than hormone-receptor positive breast cancers [2–4]. They are more common in black women and women < 40 years old [5, 6]. Twenty percent of TNBC patients will have a BRCA mutation present [7]. These tend to present aggressively with rapid growth and are often diagnosed clinically rather than

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radiographically [8]. Patients have improved disease free survival with the addition of neoadjuvant chemotherapy, especially in the locally advanced setting [9–11]. TNBC patients present with higher proliferative rates (Ki-67) and have a much poorer prognosis than receptor positive breast cancer, partly because these tumors have no targetable treatments. In fact, death within 2 years of diagnosis is much higher for women with TNBC, though survival is equivalent after 2 years [6, 11].

The publication of four randomized clinical trials [12–17] primarily guided the 2011 American Society for Radiation Oncology (ASTRO) consensus guidelines stating that (HF-WBI) should be considered in women > 50 years of age with T1-2N0 breast cancer as part of breast conserving therapy (BCT) [18]. Despite these recommendations, the uptake of HF-WBI has been slow [19–21]. Due to underrepresentation of high-grade tumors such as triple negative breast cancer (TNBC), the initial ASTRO consensus guidelines did not recommend for or against HF-WBI in this cohort. One of the four primary trials listed above showed that high grade tumors had a reduced risk of ipsilateral breast cancer recurrence with conventionally fractionated whole breast irradiation (CF-WBI) compared to HF-WBI [17], with in-breast tumor recurrences of 15.6% for HF-WBI compared to 4.7% in patients with CF-WBI. A subset analysis of this study with central pathology review showed that this difference for the high-grade tumors did not persist [22]. In 2018, a new set of guidelines was published broadening the implications of HF-WBI (Table 1), with a conditional recommendation with moderate quality of evidence to offer HF-WBI to women independent of hormone receptor status, Her2 status, and margin status [23]. In this study, we sought to identify trends over time with respect to the use of HF-WBI in TNBC women in the national cancer database (NCDB).

Materials and methods

Data source

We performed a retrospective, population-based analysis of the national cancer database (NCDB). The NCDB is jointly sponsored by the American Cancer Society and the Commission on Cancer of the American College of Surgeons that integrates highly standardized cancer registry records from more than 1500 hospitals, capturing information on 70% of all newly diagnosed malignancies in the United States, and is recognized as the largest clinical registry in the world [24]. Patient-specific data in our study includes age at diagnosis, race, year of diagnosis, insurance status, income quartile, surgery, radiation dose and dose per fraction, and receipt of neoadjuvant chemotherapy and institution (academic vs. community practice). The Commission on Cancer and American College of Surgeons note that the data are not verified and they are not responsible for the methodology used for analysis or investigator drawn conclusions.

Study cohort

Patient level data were available from the NCDB participant user file for all breast cancer diagnoses between the years of 2004 and 2013. Of the 2,032,209 patients included in the user file, we identified 53,269 TNBC women diagnosed with T1-2N0 TNBC who were > 50 years of age as outlined in our CONSORT diagram (Fig. 1) and according to the category of women who were recommended to undergo HF-WBI based on the 2011 American Society of Radiation Oncology (ASTRO) consensus guidelines. We compared rates of HF-WBI in a matched cohort of Luminal A patients who we felt represented the cohort of women most likely to be offered HF-WBI based on the consensus guideline (n = 279,757) based on identical inclusion criteria to compare rates of HF-WBI between the two cohorts in the same treatment era.

Statistical analyses

Pearson Chi square analysis was performed to compare utilization of HF-WBI between early stage (T1-2N0, age > 50) TNBC and case-matched luminal A patients. For the purposes of logistical regression analysis, treatment facility (Academic and Non-academic), race (white or black) and treatment before and after 2011 (when the ASTRO consensus guidelines were published) were dichotomized for practical comparisons. Age was assessed

Table 1 Comparison of 2011 and 2018 ASTRO consensus recommendations for HF-WBI. Adapted from 2018 ASTRO Consensus Guidelines Publication

Factor	2011	2018
Age	≥ 50 years	Any
Stage	T1-2N0	Any stage that does not require an additional field for lymph node coverage
Chemotherapy	None	Any
Dose homogeneity	± 7% in the central axis	Volume of breast tissue receiving > 105% of the prescription dose should be minimized regardless of dose-fractionation

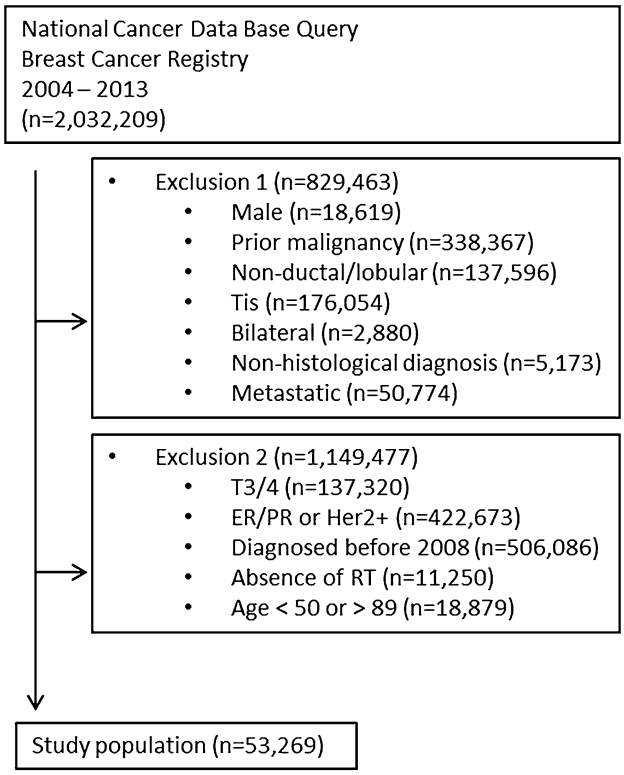

Fig. 1 Consort diagram

as a continuous variable. Income levels were separated into quartiles. Insurance was separated into the following categories: Private, Medicare, Medicaid, uninsured, government, and other. Univariate logistic regression including the above noted parameters was then undertaken to identify factors predictive of utilization of HF-WBI. Factors associated with a $p \leq 0.05$ were subsequently included in the multivariable analysis. Statistical analyses were performed using SPSS (version 24, IBM SPSS). *P* values were two-sided, and $p \leq 0.05$ were considered statistically significant.

Results

Patient and treatment characteristics for TNBC

A total of 53,269 TNBC women were identified. Patient and treatment characteristics are shown in Table 2. Trends in the utilization of HF-WBI steadily increased from 4.7% in 2008 to 14.0% in 2013 for women with TNBC, statistically significantly less than for women with luminal A cancer whose utilization increased from 7.3 to 23.3% over the same time frame ($p < 0.001$) (Fig. 2).

Table 2 Patient, tumor, and treatment characteristics

Characteristic	# (%)
Age (median, range)	58 (50–90)
Sex	
Female	53,269 (100)
Male	0 (0)
Race	
White	40,484 (76)
Black	10,121 (19)
Other	2664 (5)
Income quartile	
0–25%	6925 (13)
25–50%	8523 (16)
50–75%	14,383 (27)
75–100%	23,438 (44)
Insurance	
Private	30,363 (57)
Medicare	16,513 (31)
Medicaid	4262 (8)
Other	533 (1)
Government	533 (1)
Uninsured	1065 (2)
Vital status	
Alive	36,756 (69)
Dead	3729 (7)
Unknown	12,784 (24)
Year of diagnosis	
2008	533 (1)
2009	1589 (3)
2010	11,719 (22)
2011	13,318 (25)
2012	13,318 (25)
2013	12,792 (24)
Tumor location	
Right	25,835 (48.5)
Left	27,884 (51.5)
Histology	
Ductal carcinoma	50,605 (95)
Lobular carcinoma	2664 (5)
Grade	
1	1066 (2)
2	9588 (18)
3	42,615 (80)
LVSI	
Yes	17,579 (33)
No	35,690 (67)
Neoadjuvant chemotherapy	
Yes	5327 (10)
No	47,942 (90)
Treatment setting	
Academic	16,513 (31)
Non-academic	36,756 (69)

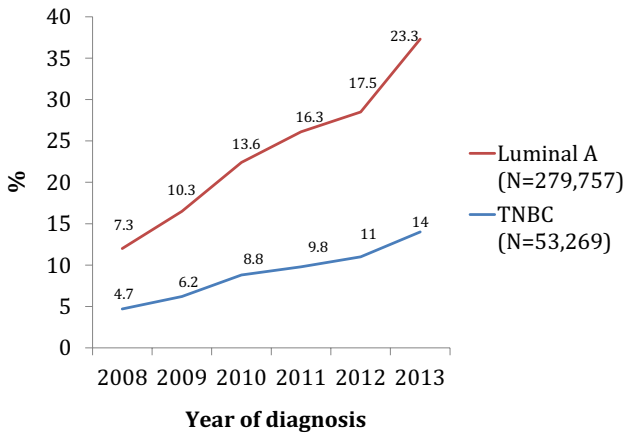

Fig. 2 Increase in Utilization of HF-WBI for TNBC vs Luminal A T1-2N0 Age > 50 Females from 2008 to 2013. Uptake for patients with TNBC was significantly slower than the uptake for patients with Luminal A breast cancer ($p < 0.01$)

Logistic regression for TNBC patients

On univariate analysis, HF-WBI was more common in older women ($p < 0.001$, OR 1.035 per year, 95% CI 1.032–1.038), women with Medicare insurance ($p < 0.001$, OR 1.968, 95% CI 1.528–2.535), higher income quartile ($p < 0.001$, OR 1.068 per quartile, 95% CI 1.031–1.107), diagnosis after 2011 ($p < 0.001$, OR 1.422, 95% CI 1.294–1.563), and women treated at academic institutions ($p < 0.001$, OR 1.674, 95% CI 1.543–1.816) (Table 3). Black race ($p = 0.041$, OR 0.905, 95% CI 0.822–0.996) and receipt of neoadjuvant chemotherapy was negatively associated with use of HF-WBI ($p < 0.001$, OR 0.605). Race did not impact the use of HF-WBI vs. CF-WBI. On multivariate analysis, age ($p < 0.001$, OR 1.038 per year, 95% CI 1.034–1.042), income quartile ($p = 0.002$, OR 1.061 per quartile, 95% CI 1.021–1.103), diagnosis after 2011 ($p < 0.001$, OR 1.418, 95% CI 1.278–1.572), and women treated at an academic institution ($p < 0.001$, OR 1.809, 95% CI 1.659–1.973) were significantly more likely to undergo HF-WBI, while women receiving neoadjuvant chemotherapy were less likely to receive HF-WBI ($p < 0.001$, OR 0.612, 95% CI 1.021–1.103) (Table 4).

Table 3 Univariate analysis for factors predictive of utilization of HF-WBI in TNBC

Factor	Odds ratio	*p*-value	95% CI
Age	1.035	**< 0.001**	1.032–1.038
Insurance status			
Private	1.173	0.211	0.914–1.507
Medicaid	1.044	0.763	0.789–1.380
Medicare	1.968	**< 0.001**	1.528–2.535
Uninsured	Ref	Ref	Ref
Other government	1.146	0.546	0.736–1.785
Treatment at academic center	1.674	**< 0.001**	1.543–1.816
Neoadjuvant chemotherapy	0.540	**< 0.001**	0.483–0.683
Median income quartile	1.068	**< 0.001**	1.031–1.107
Race			
White	Ref	**Ref**	Ref
Black	0.905	**0.041**	0.822–0.996
Diagnosis after 2011	1.422	**< 0.001**	1.294–1.563

All bold values signify statistical significance with a *p* value of < 0.05

Discussion

In this study, we demonstrate the significantly reduced uptake of HF-WBI compared to CF-WBI in TNBC patients compared to luminal A patients. The rates of uptake in TNBC increased from 4.7% in 2008 to 14.0% in 2013, with notable increases in this subset of patients, but significantly less than the increase of HF-WBI in luminal A patients which increased from 7.3 to 23.3% over the same time frame. This reduced uptake in TNBC may be attributed to the 2011 ASTRO guidelines not making recommendations for or against the use of HF-WBI in TNBC patients. This is based partly on the underrepresentation of TNBC in the 4 trials assessed in the study, as well as results from one study which suggested that those with high-grade tumors, which is commonly associated with TNBC, performed significantly better on a standard radiation regimen vs. a hypofractionated regimen [17, 18]. The patient population (ER negative) in this study was numerically underrepresented and may not definitely represent TNBC as progesterone and HER2 receptor status was not classified in the study to confirm true TNBC status of these patients. Radiobiologically, it is difficult to rationalize why hormone receptor status would influence response to therapy, or why one would expect higher dose-per-fraction as is utilized in HF-WBI to be detrimental to such a population as the response of dose-per-fraction is related to the α/β ratio of the tumor. In fact, a

Table 4 Multivariate analysis for factors predictive of utilization of HF-WBI in TNBC

Factor	Odds ratio	*p*-value	95% CI
Age	1.038	**< 0.001**	1.034–1.042
Treatment at academic center	1.809	**< 0.001**	1.659–1.973
Median income quartile	1.061	**0.002**	1.021–1.103
Diagnosis after 2011	1.418	**< 0.001**	1.278–1.572
Neoadjuvant chemotherapy	0.612	**< 0.001**	1.021–1.103

All bold values signify statistical significance with a *p* value of < 0.05

central pathology review of formalin-fixed paraffin-embedded tumor blocks on 989 women enrolled in the Canadian hypofractionated study [17] showed that basal-like (TNBC) subtype fared as well as the luminal A subtype in terms of risk of local recurrence, with Her2 positive patients suffering more local recurrences, and no difference in response to HF-WBI vs. SF-WBI on the basis of molecular subtype or tumor grade [22]. Additionally, a recent study of mice grafted with TNBC exposed to hypofractionated or standard fractionation radiation showed that secretion of decorin, a small proteoglycan of matrix with an inhibitory effect on breast cancer, was significantly increased in mice receiving hypofractionated compared to standard fractionation radiation. While we do not intend to suggest that HF-WBI is superior to SF-WBI, we do believe that the efficacy of HF-WBI is likely not hormone receptor dependent and that it is unlikely that HF-WBI is harmful to patients with TNBC.

HF-WBI has other additional benefits that may be appealing to both the patient and the treatment center. Compared to CF-WBI, HF-WBI leads to fewer total patient visits, while maintaining equivalent oncological outcomes. This affords convenience to patients, shortens the total treatment time, and reduces cost [18]. Data examining the costs of receiving HF-WBI vs. CF-WBI show an average difference of $2894 ($p < 0.001$) in hypofractionated-endorsed patients, and a difference of $8587 ($p < 0.001$) in the hypofractionated -permitted cohort [25]. Further, the shorter treatment time optimizes efficiency and throughput in the cancer center, while also shortening time to completion of all specified treatment. It has also been demonstrated that patients who receive HF-WBI may have lower acute toxic effects compared to patients those who receive conventional treatment [26]. Short-term monitoring of these patients also showed that they may suffer from less fatigue, report higher levels of energy, and have less difficulty meeting family needs 6 months post treatment [26]. The reduced treatment time and the better energy levels may allow patients to return to home and work earlier which may yield further emotional and financial benefits to the patients. Additionally, the cosmetic outcome is improved in women undergoing HF-WBI [17, 27, 28].

The 2011 ASTRO hypofractionated breast cancer guidelines were based on four randomized trials that support similar cosmetic and cancer control outcomes between HF-WBI and CF-WBI at 10-year follow-up [12, 15–17]. Due to the slow uptake in HF-WBI therapy in women with TNBC, there is a lack of literature which examines hypofractionated doses in high-grade tumors like TNBC. In the ASTRO guidelines published in 2018, there is a consensus to treat the breast cancers with HF-WBI independent of hormone receptor status and HER2 receptor status, but even so the recommendation strength is marked "conditional" and the quality of evidence for treating receptor negative tumors is deemed "moderate" [23]. Although these updated guidelines now address receptor negative tumors as a distinct subset of breast cancers, there is not a strong recommendation to prescribe HF-WBI in these patients. This may lead to continued slow uptake in HF-WBI therapy for TNBC.

HF-WBI presents a favorable option in women with early stage TNBC who have undergone optimal surgical and chemotherapeutic management. This is due to the potential financial and temporal benefits to both the patient and the treatment center. It is, therefore, important to further examine the risks and benefits of HF-WBI and to discuss it as a preferred treatment option for early stage TNBC patients, or patients not requiring comprehensive nodal coverage. Certainly, we encourage more robust evaluations of patterns of failure and overall survival in a longitudinal population of TNBC patients to confirm the safety and efficacy of this regimen, with further refinements to current recommendations at that time. We are hopeful that the results of this study highlights the slow uptake of HF-WBI in TNBC and encourages increased utilization of HF-WBI for all providers treating TNBC. We especially hope to increase utilization amongst younger patients, lower-income patients, and at centers that are not affiliated with an academic institution. This would make HF-WBI more accessible to a wider population of patients, including those from a lower income bracket. This may change the trends that we observed in our study, and be beneficial for many TNBC patients.

Conclusion

Treatment at an academic center was most correlated with increased HF-WBI in T1-2N0 TNBC women in the NCDB from 2008 to 2013, followed by increasing age and income. While HF-WBI utilization increased annually from 2008 onward, only 14% of T1-2N0 TNBC women received HF-WBI in 2013 despite similar survival with HF-WBI vs. SF-WBI. In our current healthcare climate, it is necessary to take a more value-based approach and further expand utilization of HF-WBI in TNBC. This analysis highlights the need for increased utilization amongst non-academic centers and lower income women to promote the recommendations as outlined in the updated ASTRO consensus guidelines.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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